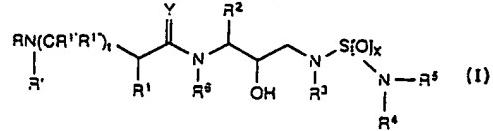
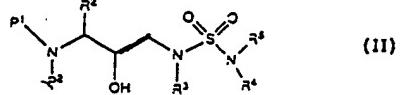


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(54) Title: HYDROXYETHYLAMINO SULFAMIC ACID DERIVATIVES USEFUL AS RETROVIRAL PROTEASE INHIBITORS		
(57) Abstract <p>Hydroxyaminoethyl sulphamic acid compounds of formulae (I) and (II), wherein R, R', R¹, R^{1'}, R^{1''}, R², R³, R⁴, R⁵, R⁶, x, t, Y, P¹ and P² are as defined in Claims 1 and 97, are effective as retroviral protease inhibitors, and in particular as inhibitors of HIV protease.</p>		
 		

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HYDROXYETHYLAMINO SULFAMIC ACID DERIVATIVES USEFUL AS RETROVIRAL PROTEASE INHIBITORS

BACKGROUND OF THE INVENTION

5

1. Field of the Invention

The present invention relates to retroviral protease inhibitors and, more particularly, relates to novel compounds and a composition and method for inhibiting retroviral proteases. This invention, in particular, relates to sulfamic acid derivatives of hydroxyethylamine protease inhibitor compounds, a composition and method for inhibiting retroviral proteases such as human immunodeficiency virus (HIV) protease and for treating a retroviral infection, e.g., an HIV infection. The subject invention also relates to processes for making such compounds as well as to intermediates useful in such processes.

20 **2. Related Art**

During the replication cycle of retroviruses, gag and gag-pol gene products are translated as proteins. These proteins are subsequently processed by a virally encoded protease (or proteinase) to yield viral enzymes and structural proteins of the virus core. Most commonly, the gag precursor proteins are processed into the core proteins and the pol precursor proteins are processed into the viral enzymes, e.g., reverse transcriptase and retroviral protease. It has been shown that correct processing of the precursor proteins by the retroviral protease is necessary for assembly of infectious viroids. For example, it has been shown that frameshift mutations in the protease region of the pol gene of HIV prevents processing of the gag precursor protein. It has also been shown through site-directed

mutagenesis of an aspartic acid residue in the HIV protease that processing of the gag precursor protein is prevented. Thus, attempts have been made to inhibit viral replication by inhibiting the action of retroviral 5 proteases.

Retroviral protease inhibition may involve a transition-state mimetic whereby the retroviral protease is exposed to a mimetic compound which binds to the 10 enzyme in competition with the gag and gag-pol proteins to thereby inhibit replication of structural proteins and, more importantly, the retroviral protease itself. In this manner, retroviral replication proteases can be effectively inhibited.

15

Several classes of compounds have been proposed, particularly for inhibition of proteases, such as for inhibition of HIV protease. Such compounds include hydroxyethylamine isosteres and reduced amide 20 isosteres. See, for example, EP O 346 847; EP O 342,541; Roberts et al, "Rational Design of Peptide-Based Proteinase Inhibitors," *Science*, 248, 358 (1990); and Erickson et al, "Design Activity, and 2.8Å Crystal Structure of a C₂ Symmetric Inhibitor Complexed to HIV-1 25 Protease," *Science*, 249, 527 (1990).

Several classes of compounds are known to be useful as inhibitors of the proteolytic enzyme renin. See, for example, U.S. No. 4,599,198; U.K. 2,184,730; 30 G.B. 2,209,752; EP O 264 795; G.B. 2,200,115 and U.S. SIR H725. Of these, G.B. 2,200,115, GB 2,209,752, EP O 264,795, U.S. SIR H725 and U.S. 4,599,198 disclose urea-containing hydroxyethylamine renin inhibitors. G.B. 2,200,115 also discloses sulfamic acid-containing 35 hydroxyethylamine renin inhibitors, and EP 0264 795 discloses certain sulfamic acid-containing

hydroxyethylamine renin inhibitors. However, it is known that, although renin and HIV proteases are both classified as aspartyl proteases, compounds which are effective renin inhibitors generally cannot be predicted 5 to be effective HIV protease inhibitors.

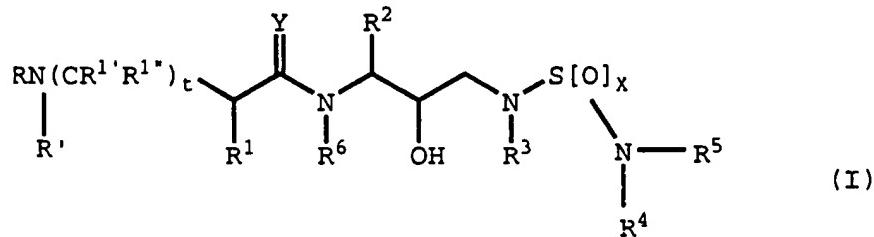
BRIEF DESCRIPTION OF THE INVENTION

10 The present invention is directed to virus inhibiting compounds and compositions. More particularly, the present invention is directed to retroviral protease inhibiting compounds and compositions, to a method of inhibiting retroviral 15 proteases, to processes for preparing the compounds and to intermediates useful in such processes. The subject compounds are characterized as sulfamic acid derivatives of hydroxyethylamine inhibitor compounds.

20 DETAILED DESCRIPTION OF THE INVENTION

In accordance with the present invention, there is provided a retroviral protease inhibiting compound of the formula:

25



or a pharmaceutically acceptable salt, prodrug or ester thereof wherein:

30

R represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, alkoxycarbonyl, aryloxyalkyl, heteroaryloxyalkyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, 5 cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclcarbonyl, heterocycloxycarbonyl, heterocyclalkanoyl, heterocyclalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, 10 heteroaryloxycarbonyl, heteroaroyl, hydroxalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, 15 heteraryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyl radicals, or wherein said aminocarbonyl and aminoalkanoyl radicals are disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl 20 or heteraryl radical;

R' represents hydrogen, radicals as defined for R³ or R"SO₂- wherein R" represents radicals as defined for R³; or R and R' together with the nitrogen to which they are 25 attached represent heterocycloalkyl and heteraryl radicals;

R¹ represents hydrogen, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃, -CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), 30 -C(CH₃)₂(SC₆H₅), -C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and methionine and the sulfoxide (SO) and sulfone (SO₂) derivatives thereof, 35 isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine,

glutamine, threonine, glycine, allo-threonine, serine, O-alkyl serine, aspartic acid, beta-cyanoalanine and valine side chains;

- 5 R^{1'} and R^{1"} independently represent hydrogen and radicals as defined for R¹, or one of R^{1'} and R^{1"}, together with R¹ and the carbon atoms to which R¹, R^{1'} and R^{1"} are attached, represent a cycloalkyl radical;
- 10 R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radials, -NO₂, -CN, -CF₃, -OR⁹ and -SR⁹, wherein R⁹ represents hydrogen and alkyl radicals;
- 15 R³ represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone and sulfoxide derivatives thereof;
- 30 R⁴ and R⁵ independently represent hydrogen and radicals as defined by R³ or together with a nitrogen atom to which they are bonded form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and

aryl radicals and the sulfone and sulfoxide derivatives thereof;

R⁶ represents hydrogen and alkyl radicals;

5

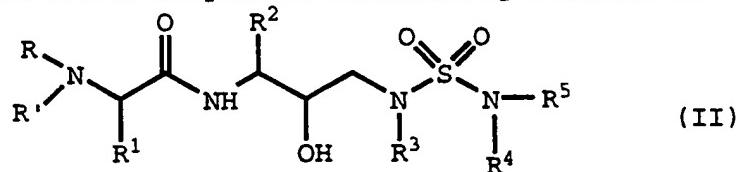
x represents 1 or 2;

t represents either 0, 1 or 2; and

10 Y represents O, S and NR¹⁵ wherein R¹⁵ represents hydrogen and radicals as defined for R³.

A family of compounds of particular interest within Formula I are compounds embraced by Formula II:

15



wherein:

R represents hydrogen, alkyl, alkenyl, cycloalkyl, hydroxyalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, alkoxycarbonyl, alkoxyalkyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclcarbonyl, heterocyclalkanoyl, heterocyclalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted 30 aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl.

heterocycloalkyl, heterocycloalkyalkyl radicals, or where said aminoalkanoyl radical or aminocarbonyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl
5 or heteroaryl radical;

R' represents hydrogen and radicals as defined for R³ or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl
10 radical;

R¹ represents hydrogen, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃, -CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂(SC₆H₅), -C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃),
15 alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine and methionine and the sulfoxide (SO) and sulfone (SO₂) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-
20 leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine, O-methyl serine, aspartic acid, beta-cyanoalanine and valine side chains;

25 R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, -NO₂, -C≡N, CF₃, -OR⁹, -SR⁹, wherein R⁹ represents hydrogen and alkyl radicals;

30 R³ represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and
35 disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl,

- cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they
5 are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone or sulfoxide derivatives thereof;
- 10 R⁴ and R⁵ independently represent hydrogen and radicals as defined by R³, or together with the nitrogen atom to which they are bonded represent heterocycloalkyl and heteroaryl radicals.
- 15 A more preferred family of compounds within Formula II consists of compounds wherein:
- R represents hydrogen, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl,
20 cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclcarbonyl, heterocyclloxy carbonyl, heterocyclalkanoyl, heterocyclalkoxycarbonyl,
25 heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy carbonyl, heteroarooyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are
30 selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals, or where said aminocarbonyl or aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen
35 atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R³ or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl

5 radical;

R¹ represents CH₂C(O)NHCH₃, C(CH₃)₂(SCH₃), C(CH₃)₂(S[O]CH₃), C(CH₃)₂(S[O]₂CH₃), alkyl, alkenyl and alkynyl radicals, and amino acid side chains selected
10 from the group consisting of asparagine, valine, threonine, allo-threonine, isoleucine, tert-leucine, S-methyl cysteine and methionine and the sulfone and sulfoxide derivatives thereof, alanine, and allo-isoleucine;

15

R² represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula -OR⁹ and -SR⁹ wherein R⁹ represents alkyl radicals; and

20

R³ represents alkyl, haloalkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals; and

25

R⁴ and R⁵ independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkyl and heterocycloalkylalkyl radicals, or R⁴ and R⁵ together with the nitrogen atom to
30 which they are bonded from a heterocycloalkyl or heteroaryl radical.

Of highest interest are compounds within Formula II wherein

- R represents alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl,
- 5 aryloxyalkanoyl, heterocyclcarbonyl, heterocyclyloxycarbonyl, heterocyclalkanoyl, heterocyclalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, aminocarbonyl, aminoalkanoyl, and mono- and
- 10 disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyl radicals, or where
- 15 said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;
- 20 R' represents hydrogen and radicals as defined for R³ or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;
- 25 R¹ represents CH₂C(O)NHCH₃, C(CH₃)₂(SCH₃), C(CH₃)₂(S[O]CH₃), C(CH₃)₂(S[O]₂CH₃), methyl, propargyl, t-butyl, isopropyl and sec-butyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, S-methyl cysteine, allo-iso-leucine,
- 30 iso-leucine, and beta-cyano alanine side chains;
- R² represents CH₃SCH₂CH₂-, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals;

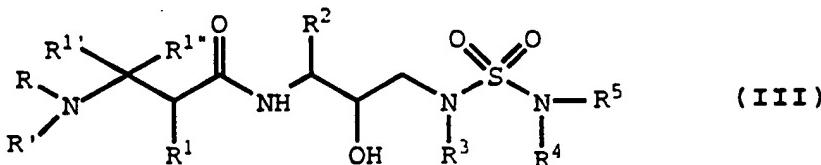
R³ represents propyl, isoamyl, n-butyl, isobutyl, cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl radicals; and

- 5 R⁴ and R⁵ independently represent hydrogen and methyl, ethyl, i-propyl, n-butyl, t-butyl, 1,1-dimethylpropyl and phenyl radicals, or together with the nitrogen atom to which they are bonded form a pyrrolidinyl, piperidinyl, morpholinyl, piperazinyl or N'-alkylpiperazinyl radical.

10

Another family of compounds of particular interest within Formula I are compounds embraced by Formula III:

15



wherein:

- R represents hydrogen, alkoxy carbonyl, aralkoxy carbonyl, alkyl carbonyl, cycloalkyl carbonyl,
20 cycloalkyl alkoxy carbonyl, cycloalkyl alkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclic carbonyl, heterocyclic oxycarbonyl, heterocyclic lalkanoyl, heterocyclic lalkoxy carbonyl, heteroaralkanoyl, heteroaralkoxy carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl
25 radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals, or where said
30

aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

5 R' represents hydrogen and radicals as defined for R³ or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

10 R¹ represents hydrogen, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃, -CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine 15 and methionine and the sulfoxide (SO) and sulfone (SO₂) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine, aspartic acid, beta-cyano alanine 20 and valine side chains;

R^{1'} and R^{1''} independently represent hydrogen and radicals as defined for R¹, or one of R^{1'} and R^{1''}, together with R¹ and the carbon atoms to which R¹, R^{1'} and R^{1''} are 25 attached, represent a cycloalkyl radical;

R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radials, -NO₂, -C≡N, CF₃, -OR⁹ and -SR⁹, wherein R⁹ 30 represents hydrogen and alkyl radicals;

R³ represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, 35 heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and

disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or
5 in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone or sulfoxide derivatives
10 thereof;

R⁴ and R⁵ independently represent hydrogen and radicals as defined by R³, or together with the nitrogen atom to which they are bonded represent heterocycloalkyl and
15 heteroaryl radicals.

A more preferred family of compounds within Formula III consists of compounds wherein

20 R represents an arylalkanoyl, heteroaroyl, aryloxyalkanoyl, aryloxycarbonyl, alkanoyl, aminocarbonyl, mono-substituted aminoalkanoyl, or disubstituted aminoalkanoyl, or mono- or dialkylaminocarbonyl radical;
25 R' represents hydrogen and radicals as defined for R³ or R and R' together with the nitrogen to which they are attached represent a heterocycloalkyl or heteroaryl radical;
30 R¹, R^{1'} and R^{1''} independently represent hydrogen and alkyl radicals having from 1 to about 4 carbon atoms, alkenyl, alkynyl, aralkyl radicals, and radicals represented by the formula -CH₂C(O)R" or -C(O)R" wherein
35 R" represents R³⁸, -NR³⁸R³⁹ and OR³⁸ wherein R³⁸ and R³⁹

independently represent hydrogen and alkyl radicals having from 1 to about 4 carbon atoms;

- R² represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula -OR⁹ and -SR⁹ wherein R⁹ represents hydrogen and alkyl radicals; and
- 5 10 R³ represents alkyl, haloalkyl, alkenyl, alkynyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl radicals; and
- 15 20 R⁴ and R⁵ independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkyl and heterocycloalkylalkyl radicals, or R⁴ and R⁵ together with the nitrogen atom to which they are bonded from a heterocycloalkyl or heteroaryl radical.

Of highest interest are compounds of Formula III wherein:

- 25 R represents an arylalkanoyl, aryloxycarbonyl, aryloxyalkanoyl, alkanoyl, aminocarbonyl, mono-substituted aminoalkanoyl, or disubstituted aminoalkanoyl, or mono-or dialkylaminocarbonyl radical;
- 30 R' represents hydrogen and radicals as defined for R³ or R and R' together with the nitrogen to which they are attached represent a heterocycloalkyl or heteroaryl radical;

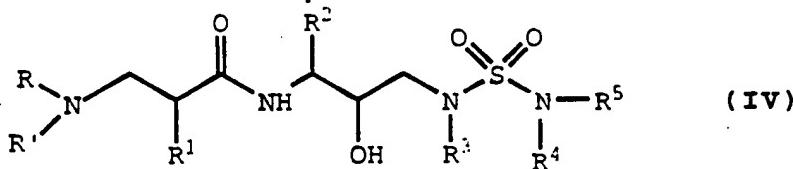
R₁, R_{1'} and R_{1''} independently represent hydrogen, methyl, ethyl, benzyl, phenylpropyl, -C(O)NH₂ and propargyl radicals;

5 R² represents CH₃SCH₂CH₂-, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals;

10 R³ represents propyl, isobutyl, isoamyl, n-butyl, cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl radicals; and

15 R⁴ and R⁵ independently represent hydrogen and methyl, ethyl, i-propyl, n-butyl, t-butyl, 1,1-dimethylpropyl, cyclohexyl and phenyl radicals, or together with the nitrogen atom to which they are bonded form a pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl radical.

20 Another family of compounds of particular interest within Formula I are compounds embraced by Formula IV:



25

wherein:

30 R represents hydrogen, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, alkoxy carbonyl, aralkoxy carbonyl, alkyl carbonyl, cycloalkyl carbonyl, cycloalkylalkoxy carbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxy carbonylalkyl, aryloxyalkanoyl,

- heterocyclylcarbonyl, heterocyclyloxycarbonyl,
heterocyclylalkanoyl, heterocyclylalkoxycarbonyl,
heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-
carbonyl, heteroaroyl, aminocarbonyl, aminoalkanoyl, and
5 mono- and disubstituted aminocarbonyl and mono- and
disubstituted aminoalkanoyl radicals wherein the
substituents are selected from alkyl, aryl, aralkyl,
cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl,
heterocycloalkyl, heterocycloalkylalkyl radicals, or where
10 said aminoalkanoyl radical is disubstituted, said
substituents along with the nitrogen atom to which they
are attached form a heterocycloalkyl or heteroaryl
radical;
- 15 R' represents hydrogen and radicals as defined for R³ or
R and R' together with the nitrogen to which they are
attached represent heterocycloalkyl and heteroaryl
radical;
- 20 R¹ represents hydrogen, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃,
-CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃),
-C(CH₃)₂(SC₆H₅), -C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃),
alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl
radicals, and amino acid side chains selected from
25 asparagine, S-methyl cysteine and methionine and the
sulfoxide (SO) and sulfone (SO₂) derivatives thereof,
isoleucine, allo-isoleucine, alanine, leucine, tert-
leucine, phenylalanine, ornithine, histidine, norleucine,
glutamine, threonine, glycine, allo-threonine, serine,
30 aspartic acid, beta-cyano alanine and valine side
chains;
- R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl
and aralkyl radicals, which radicals are optionally
35 substituted with a group selected from alkyl and halogen

radicals, -NO₂, -C≡N, CF₃, -OR⁹, -SR⁹, wherein R⁹ represents hydrogen and alkyl;

- R³ represents alkyl, haloalkyl, alkenyl, alkynyl,
5 hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl,
10 cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl
15 radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone or sulfoxide derivatives thereof;

- R⁴ and R⁵ independently represent hydrogen and radicals
20 as defined for R³ or together with a nitrogen atom to which they are bonded form a heterocycloalkyl or a heteroaryl radical.

- A more preferred family of compounds within
25 Formula IV consists of compounds wherein

- R represents hydrogen, alkoxycarbonyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl,
30 cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, arakanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclcarbonyl, heterocyclalkanoyl, heterocyclloxy carbonyl, heterocyclalkoxy carbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl,
35 heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl,

aryloxyalkyl, heteroaryloxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from

5 alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached

10 form a heterocycloalkyl or heteroaryl radical;

R' represents hydrogen and radicals as defined for R³ or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl

15 radical;

R¹ represents hydrogen, alkyl and alkenyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, threonine, allo-threonine,

20 isoleucine, tert-leucine, S-methyl cysteine and the sulfone and sulfoxide derivatives thereof, alanine, and allo-isoleucine;

R² represents alkyl, cycloalkylalkyl and aralkyl

25 radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula -OR⁹ and -SR⁹ wherein R⁹ represents hydrogen and alkyl and halogen radicals;

30 R³ represents alkyl, halalkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl, heteroaryl and heteroaralkyl radicals; and

35 R⁴ and R⁵ independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl,

heteroaralkyl, heterocycloalkyl and heterocycloalkylalkyl radicals, or R⁴ and R⁵ together with the nitrogen atom to which they are bonded from a heterocycloalkyl or heteroaryl radical.

5

Of highest interest are compounds within Formula IV wherein

- R represents hydrogen, alkoxy carbonyl, aralkoxy carbonyl,
10 alkyl carbonyl, cycloalkyl carbonyl, cycloalkylalkoxy carbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclyl carbonyl, heterocyclyloxy carbonyl, heterocyclylalkanoyl,
15 heterocyclylalkoxy carbonyl, heteroaralkanoyl, heteroaralkoxy carbonyl, heteroaryl oxy carbonyl, heteroaroyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are
20 selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they
25 are attached form a heterocycloalkyl or heteroaryl radical;

- R' represents hydrogen and radicals as defined for R³ or R and R' together with the nitrogen to which they are
30 attached represent heterocycloalkyl and heteroaryl radical;

- R¹ represents hydrogen, methyl, propargyl, t-butyl, isopropyl and sec-butyl radicals, and amino acid side
35 chains selected from the group consisting of asparagine, valine, S-methyl cysteine, allo-iso-leucine, iso-leucine,

threonine, serine, aspartic acid, beta-cyano alanine, and allo-threonine side chains;

R² represents CH₃SCH₂CH₂-, iso-butyl, n-butyl, benzyl,
5 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl
radicals;

R³ represents propyl, isobutyl, isoamyl, n-butyl,
10 cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl
radicals; and

R⁴ and R⁵ independently represent hydrogen and methyl,
ethyl, i-propyl, n-butyl, t-butyl, 1,1-dimethylpropyl,
15 cyclohexyl and phenyl radicals, or R⁴ and R⁵ together
with the nitrogen atom to which they are bonded form a
pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl
radical.

As utilized herein, the term "alkyl", alone or
20 in combination, means a straight-chain or branched-chain
alkyl radical containing from 1 to about 10, preferably
from 1 to 8, carbon atoms. Examples of such radicals
include methyl, ethyl, n-propyl, isopropyl, n-butyl,
isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl,
25 octyl and the like. The term "alkenyl", alone or in
combination, means a straight-chain or branched-chain
hydrocarbon radical having one or more double bonds and
containing from 2 to about 18 carbon atoms preferably
from 2 to 8 carbon atoms. Examples of suitable alkenyl
30 radicals include ethenyl, propenyl, 1,4-butadienyl,
12-octadecene and the like. The term "alkynyl", alone or
in combination, means a straight-chain hydrocarbon
radical having one or more triple bonds and containing
from 2 to about 10 carbon atoms, preferably from 2 to 8
35 carbon atoms. Examples of alkynyl radicals include
ethynyl, propynyl, (propargyl), butynyl and the like.

The term "alkoxy", alone or in combination, means an alkyl ether radical wherein the term alkyl is as defined above. Examples of suitable alkyl ether radicals include methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy and the like. The term "cycloalkyl", alone or in combination, means a saturated or partially saturated monocyclic, bicyclic or tricyclic alkyl radical wherein each cyclic moiety contains from about 3 to about 8 carbon atoms and is cyclic. The term "cycloalkylalkyl" means an alkyl radical as defined above which is substituted by a cycloalkyl radical containing from about 3 to about 8, preferably from 3 to 6 carbon atoms. Examples of such cycloalkyl radicals include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and the like. The term "aryl", alone or in combination, means a phenyl or naphthyl radical which optionally carries one or more substituents selected from alkyl, alkoxy, halogen, hydroxy, amino, nitro, cyano, haloalkyl and the like, such as phenyl, p-tolyl, 4-methoxyphenyl, 4-(tert-butoxy)phenyl, 4-fluorophenyl, 4-chlorophenyl, 4-hydroxyphenyl, 1-naphthyl, 2-naphthyl, and the like. The term "aralkyl", alone or in combination, means an alkyl radical as defined above in which one hydrogen atom is replaced by an aryl radical as defined above, such as benzyl, 2-phenylethyl and the like. The term "aralkoxy carbonyl", alone or in combination, means a radical of the formula -C(O)-O-aralkyl in which the term "aralkyl" has the significance given above. An example of an aralkoxycarbonyl radical is benzyloxycarbonyl. The term "aryloxy" means a radical of the formula aryl-O- in which the term aryl has the significance given above. The term "alkanoyl", alone or in combination, means an acyl radical derived from an alkanecarboxylic acid wherein alkane means a radical as defined above for alkyl. Examples of alkanoyl radicals include acet, 1, propionyl.

butyryl, valeryl, 4-methylvaleryl, and the like. The term "cycloalkylcarbonyl" means an acyl group derived from a monocyclic or bridged cycloalkanecarboxylic acid such as cyclopropanecarbonyl, cyclohexanecarbonyl,

5 adamantanecarbonyl, and the like, or from a benz-fused monocyclic cycloalkanecarboxylic acid which is optionally substituted by, for example, alkanoylamino, such as 1,2,3,4-tetrahydro-2-naphthoyl,2-acetamido-1,2,3,4-tetrahydro-2-naphthoyl. The term "aralkanoyl" means an

10 acyl radical derived from an aryl-substituted alkanecarboxylic acid such as phenylacetyl, 3-phenylpropionyl (hydrocinnamoyl), 4-phenylbutyryl, (2-naphthyl)acetyl, 4-chlorohydrocinnamoyl, 4-aminohydrocinnamoyl, 4-methoxyhydrocinnamoyl, and the like.

15 The term "aroyle" means an acyl radical derived from an aromatic carboxylic acid. Examples of such radicals include aromatic carboxylic acids, an optionally substituted benzoic or naphthoic acid such as benzoyl, 4-chlorobenzoyl, 4-carboxybenzoyl,

20 4-(benzyloxycarbonyl)benzoyl, 1-naphthoyl, 2-naphthoyl, 6-carboxy-2 naphthoyl, 6-(benzyloxycarbonyl)-2-naphthoyl, 3-benzyloxy-2-naphthoyl, 3-hydroxy-2-naphthoyl, 3-(benzyloxyformamido)-2-naphthoyl, and the like. The heterocyclyl or heterocycloalkyl portion of a

25 heterocyclylcarbonyl, heterocycloloxycarbonyl, heterocyclalkoxycarbonyl, or heterocyclalkyl group or the like is a saturated or partially unsaturated monocyclic, bicyclic or tricyclic heterocycle which contains one or more hetero atoms selected from nitrogen,

30 oxygen and sulphur, which is optionally substituted on one or more carbon atoms by halogen, alkyl, alkoxy, oxo, and the like, and/or on a secondary nitrogen atom (i.e., -NH-) by alkyl, aralkoxycarbonyl, alkanoyl, phenyl or phenylalkyl or on a tertiary nitrogen atom (i.e. = N-) by

35 oxido and which is attached via a carbon atom. The heteroaryl portion of a heteroaroyl,

heteroaryloxycarbonyl, or a heteroaralkoxy carbonyl group or the like is an aromatic monocyclic, bicyclic, or tricyclic heterocycle which contains the hetero atoms and is optionally substituted as defined above with respect to the definition of heterocyclyl. Such heterocyclyl and heteroaryl radicals have from four to about 12 ring members, preferably from 4 to 10 ring members. Examples of such heterocyclyl and heteroaryl groups are pyrrolidinyl, piperidinyl, piperazinyl, morpholinyl, thiamorpholinyl, pyrrolyl, imidazolyl (e.g., imidazol 4-yl, 1-benzyloxycarbonylimidazol-4-yl, etc.), pyrazolyl, pyridyl, pyrazinyl, pyrimidinyl, furyl, thienyl, triazolyl, oxazolyl, thiazolyl, indolyl (e.g., 2-indolyl, etc.), quinolinyl, (e.g., 2-quinolinyl, 3-quinolinyl, 15 1-oxido-2-quinolinyl, etc.), isoquinolinyl (e.g., 1-isoquinolinyl, 3-isoquinolinyl, etc.), tetrahydroquinolinyl (e.g., 1,2,3,4-tetrahydro-2-quinolyl, etc.), 1,2,3,4-tetrahydroisoquinolinyl (e.g., 1,2,3,4-tetrahydro-1-oxo-isoquinolinyl, etc.), 20 quinoxalinyl, β -carbolinyl, 2-benzofurancarbonyl, 1-, 2-, 4- or 5-benzimidazolyl, and the like. The term "cycloalkylalkoxycarbonyl" means an acyl group derived from a cycloalkylalkyl-O-COOH wherein cycloalkylalkyl has the significance given above. The term "aryloyalkanoyl" means an acyl radical of the formula aryl-O-alkanoyl wherein aryl and alkanoyl have the significance given above. The term "heterocyclloxycarbonyl" means an acyl group derived from heterocyclyl-O-COOH wherein heterocyclyl is as defined above. The term "heterocyclalkanoyl" is an acyl radical derived from a heterocyclyl-substituted alkane carboxylic acid wherein heterocyclyl has the significance given above. The term "heterocyclalkoxycarbonyl" means an acyl radical derived from a heterocyclyl-substituted alkane-O-COOH wherein heterocyclyl has the significance given above.

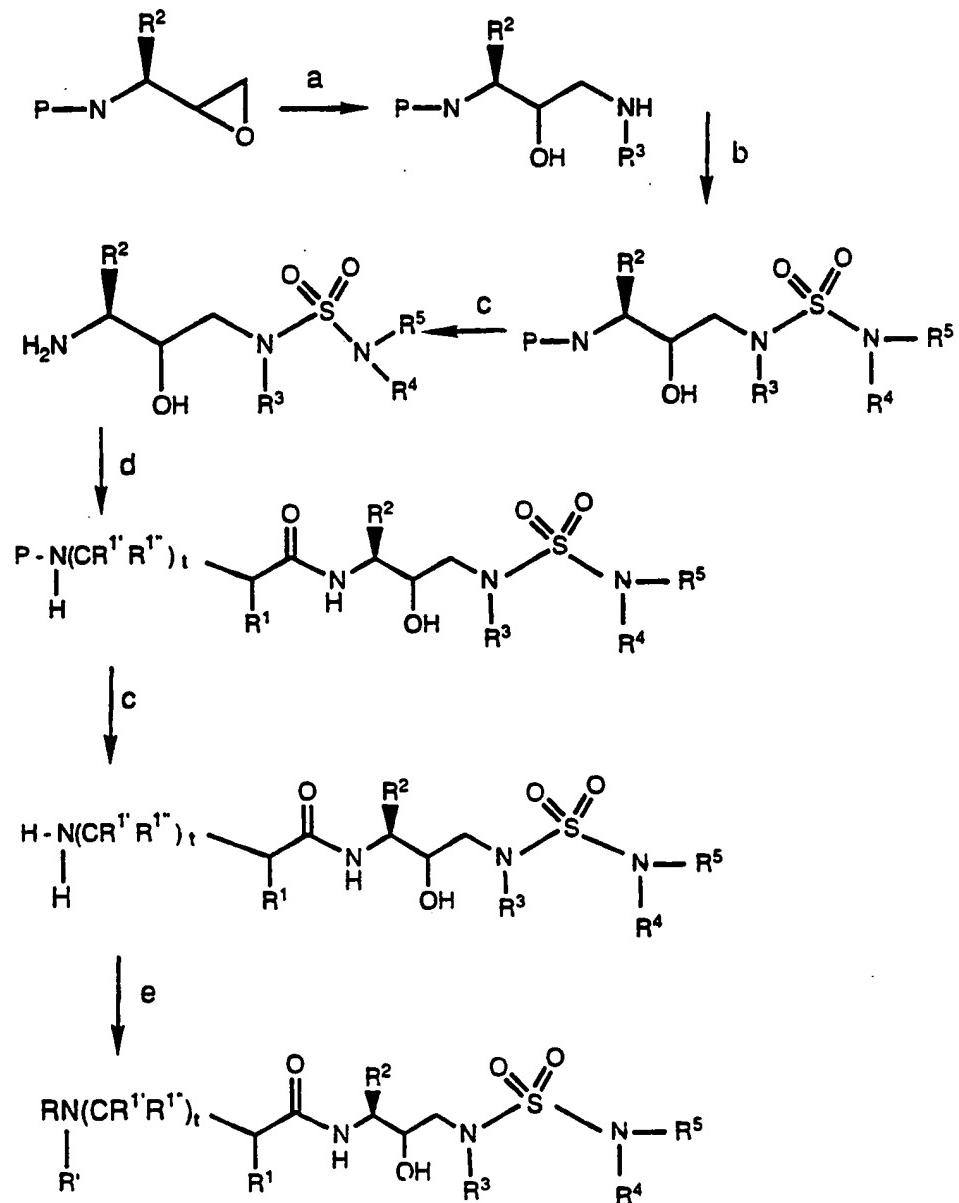
The term "heteroaryloxycarbonyl" means an acyl radical derived from a carboxylic acid represented by heteroaryl-O-COOH wherein heteroaryl has the significance given above. The term "aminocarbonyl" alone or in combination, 5 means an amino-substituted carbonyl (carbamoyl) group derived from an amino-substituted carboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from hydrogen, and alkyl, aryl, aralkyl, cycloalkyl, 10 cycloalkylalkyl radicals and the like. The term "aminoalkanoyl" means an acyl group derived from an amino-substituted alkanecarboxylic acid wherein the amino group can be a primary, secondary or tertiary amino group containing substituents selected from hydrogen, and 15 alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl radicals and the like. The term "halogen" means fluorine, chlorine, bromine or iodine. The term "haloalkyl" means an alkyl radical having the significance as defined above wherein one or more 20 hydrogens are replaced with a halogen. Examples of such haloalkyl radicals include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl and the like. The term "leaving group" generally refers to groups readily displaceable by 25 a nucleophile, such as an amine, a thiol or an alcohol nucleophile. Such leaving groups are well known in the art. Examples of such leaving groups include, but are not limited to, N-hydroxysuccinimide, N-hydroxybenzotriazole, halides, triflates tosylates and 30 the like. Preferred leaving groups are indicated herein where appropriate.

Procedures for preparing the compounds of Formula I are set forth below. It should be noted that 35 the general procedure is shown as it relates to preparation of compounds having the specified

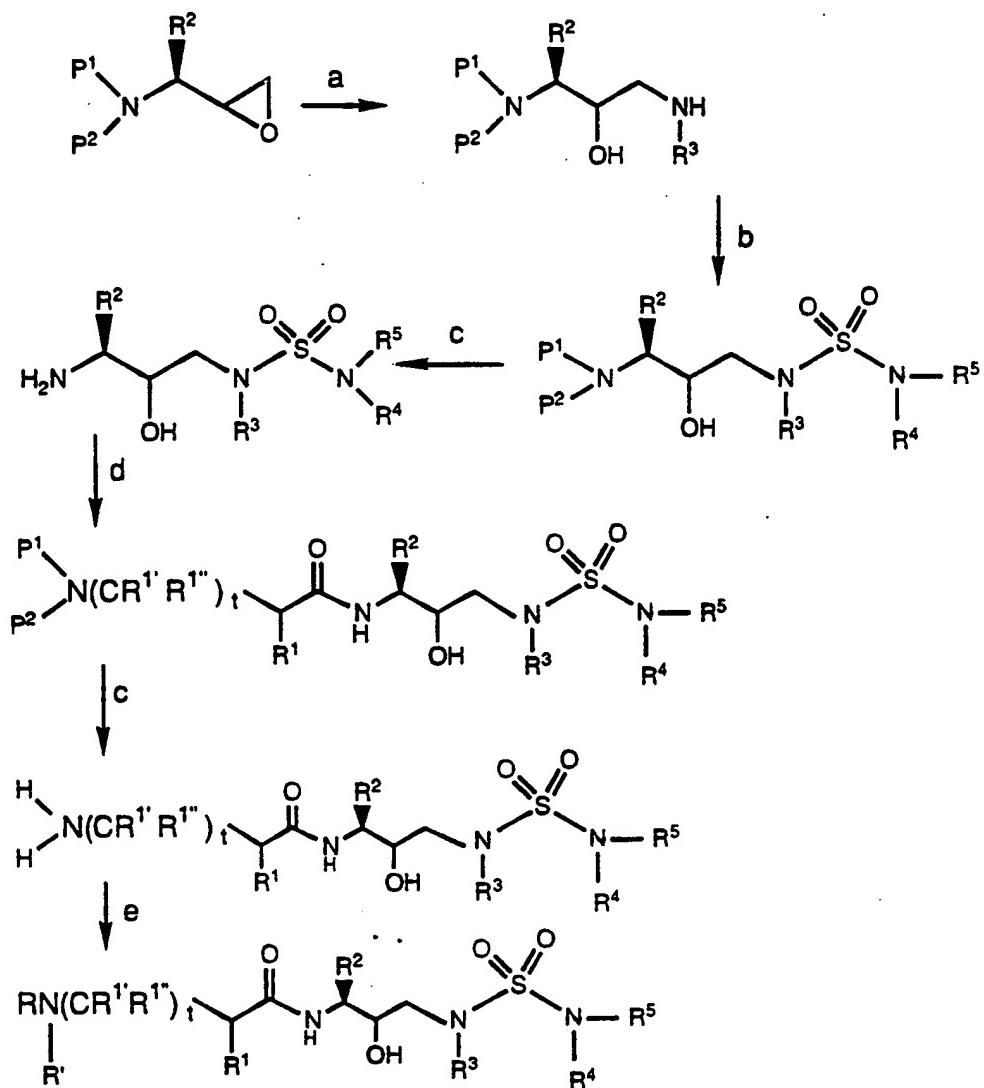
stereochemistry, for example, wherein the absolute stereochemistry about the hydroxyl group is designated as (R), which is the preferred stereochemistry for the compounds of the present invention. However, such procedures are generally applicable to those compounds of opposite configuration, e.g., where the stereochemistry about the hydroxyl group is (S). In addition, the compounds having the (R) stereochemistry can be utilized to produce those having the (S) stereochemistry. For example, a compound having the (R) stereochemistry can be inverted to the (S) stereochemistry using well-known methods.

15 Preparation of Compounds of Formula I

The compounds of the present invention represented by Formula I above can be prepared utilizing the following general procedure. This procedure is 20 schematically shown in the following Schemes I and II:

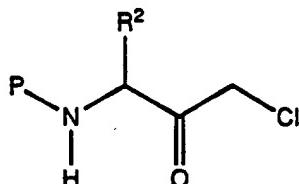
SCHEME I

- a) amine b) sulfamoyl chloride R⁴R⁵NSO₂Cl (or anhydride)
 + acid scavenger c) deprotection d) coupling
 e) coupling.

SCHEME II

- a) amine
- b) sulfamoyl chloride $R^4 R^5 NSO_2 Cl$ (or anhydride)
+ acid scavenger
- c) deprotection
- d) coupling
- e) coupling.

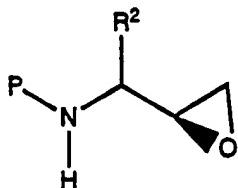
An N-protected chloroketone derivative of an amino acid having the formula:



5

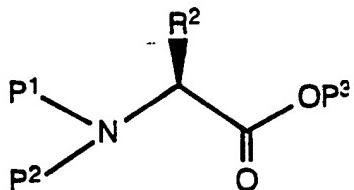
- wherein P represents an amino protecting group, and R² is as defined above, is reduced to the corresponding alcohol utilizing an appropriate reducing agent. Suitable amino protecting groups are well known in the art and include carbobenzoxy, t-butoxycarbonyl, and the like. A preferred amino protecting group is carbobenzoxy. A preferred N-protected chloroketone is N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone. A preferred reducing agent is sodium borohydride. The reduction reaction is conducted at a temperature of from -10°C to about 25°C, preferably at about 0°C, in a suitable solvent system such as, for example, tetrahydrofuran, and the like. The N-protected chloroketones are commercially available, e.g., such as from Bachem, Inc., Torrance, California.
- Alternatively, the chloroketones can be prepared by the procedure set forth in S. J. Fittkau, J. Prakt. Chem., 315, 1037 (1973), and subsequently N-protected utilizing procedures which are well known in the art.
- The halo alcohol can be utilized directly, as described below, or, preferably, is then reacted, preferably at room temperature, with a suitable base in a suitable solvent system to produce an N-protected amino epoxide of the formula:

25
30



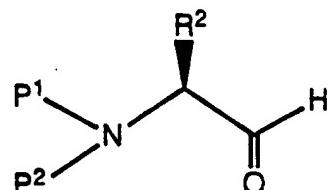
wherein P and R² are as defined above. Suitable solvent systems for preparing the amino epoxide include ethanol, methanol, isopropanol, tetrahydrofuran, dioxane, and the like including mixtures thereof. Suitable bases for producing the epoxide from the reduced chloroketone include potassium hydroxide, sodium hydroxide, potassium t-butoxide, DBU and the like. A preferred base is potassium hydroxide.

Alternatively, a protected amino epoxide can be prepared starting with an L-amino acid which is reacted with a suitable amino-protecting group in a suitable solvent to produce an amino-protected L-amino acid ester of the formula:



wherein P¹ and P² independently represent hydrogen, benzyl and amino-protecting groups (as defined above), provided that P¹ and P² are not both hydrogen; P³ represents carboxyl-protecting group, e.g., methyl, ethyl, benzyl, tertiary-butyl and the like; and R² is as defined above.

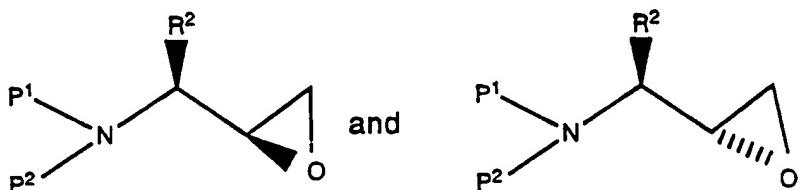
The amino-protected L-amino acid ester is then reduced, to the corresponding alcohol. For example, the amino-protected L-amino acid ester can be reduced with diisobutylaluminum hydride at -78° C in a suitable solvent such as toluene. The resulting alcohol is then converted, for example, by way of a Swern oxidation, to the corresponding aldehyde of the formula:



10

wherein P¹, P² and R² are as defined above. Thus, a dichloromethane solution of the alcohol is added to a cooled (-75 to -68° C) solution of oxalyl chloride in dichloromethane and DMSO in dichloromethane and stirred for 35 minutes.

The aldehyde resulting from the Swern oxidation is then reacted with a halomethylolithium reagent, which reagent is generated *in situ* by reacting an alkyllithium or aryllithium compound with a dihalomethane represented by the formula X¹CH₂X² wherein X¹ and X² independently represent I, Br or Cl. For example, a solution of the aldehyde and chloroiodomethane in THF is cooled to -78° C and a solution of n-butyllithium in hexane is added. The resulting product is a mixture of diastereomers of the corresponding amino-protected epoxides of the formulas:



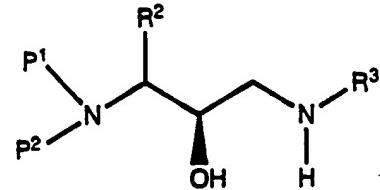
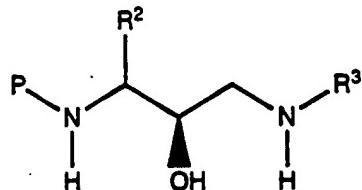
The diastereomers can be separated e.g., by chromatography, or, alternatively, once reacted in subsequent steps the diastereomeric products can be separated. For compounds having the (S) stereochemistry,

- 5 a D-amino acid can be utilized in place of the L-amino acid.

The amino epoxide is then reacted, in a suitable solvent system, with an equal amount, or preferably an 10 excess of, a desired amine of the formula:



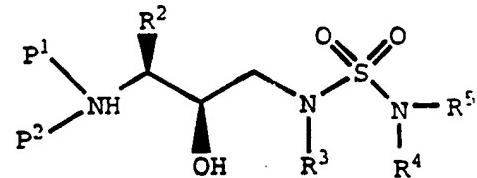
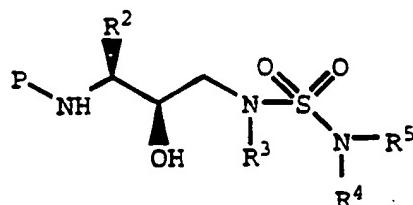
wherein R^3 is hydrogen or is as defined above. The 15 reaction can be conducted over a wide range of temperatures, e.g., from about 10°C to about 100°C, but is preferably, but not necessarily, conducted at a temperature at which the solvent begins to reflux. Suitable solvent systems include protic, non-protic and 20 dipolar aprotic organic solvents such as, for example, those wherein the solvent is an alcohol, such as methanol, ethanol, isopropanol, and the like, ethers such as tetrahydrofuran, dioxane and the like, and toluene, N,N-dimethylformamide, dimethyl sulfoxide, and mixtures 25 thereof. A preferred solvent is isopropanol. Exemplary amines corresponding to the formula R^3NH_2 include benzyl amine, isobutylamine, n-butyl amine, isopentyl amine, isoamylamine, cyclohexanemethyl amine, naphthylene methyl amine and the like. The resulting product is a 3-(N- 30 protected amino)-3-(R^2)-1-(NHR^3)-propan-2-ol derivative (hereinafter referred to as an amino alcohol) can be represented by the formulas:



wherein P, P¹, P², R² and R³ are as described above.

Alternatively, a haloalcohol can be utilized in place of
5 the amino epoxide.

The amino alcohol defined above is then reacted in a suitable solvent with a sulfamoyl halide, e.g. sulfamoyl chloride ($R^4R^5NSO_2Cl$ or R^4HNSO_2Cl) or sulfamoyl 10 anhydride in the presence of an acid scavenger. Suitable solvents in which the reaction can be conducted include methylene chloride, tetrahydrofuran. Suitable acid scavengers include triethylamine, pyridine. The resulting sulfamic acid derivative can be represented, depending on 15 the epoxide utilized, by the formulas;



wherein P, P¹, P², R², R³, R⁴ and R⁵ are as defined above.

20 These intermediates are useful for preparing inhibitor compounds of the present invention and are also active inhibitors of retroviral proteases.

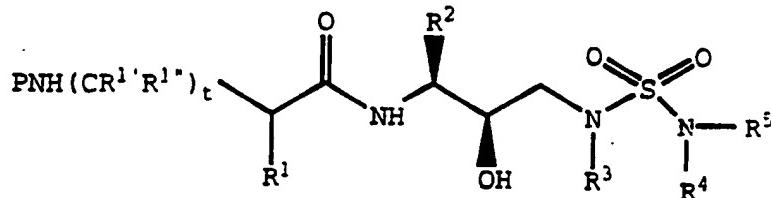
The sulfamoyl halides of the formula R^4NHSO_2X 25 can be prepared by the reaction of a suitable isocyanate of the formula R^4NCO with fuming sulfuric acid to produce the corresponding sulfamate which is then converted to the halide by well known procedures, such as by treating the

sulfamate with PCl_5 . Alternatively the isocyanate can be treated with chlorosulfonic acid to produce the corresponding sulfamoyl chloride directly.

5 The sulfamoyl halides of the formula $\text{R}^4\text{R}^5\text{NSO}_2\text{Cl}$ can be prepared by reacting an amine of the formula $\text{R}^4\text{R}^5\text{NH}$, preferably as a salt such as the hydrochloride, with sulfonyl chloride in a suitable solvent such as acetonitrile. The reaction mixture is gradually warmed to
10 reflux temperature and maintained at the reflux temperature until the reaction is complete.
 Alternatively, sulfamoyl halides of the formula $\text{R}^4\text{R}^5\text{NSO}_2\text{Cl}$ can be prepared by reacting an amine of the formula $\text{R}^4\text{R}^5\text{NH}$ with sulfonyl chloride in boiling MeCN as disclosed in
15 Matier et al., J. Med. Chem., 15, No. 5, p.538 (1972).

Following preparation of the sulfamic acid derivative, the amino protecting group P or P^1 and P^2 amino protecting groups are removed under conditions which will not affect the remaining portion of the molecule.
20 These methods are well known in the art and include acid hydrolysis, hydrogenolysis and the like. A preferred method involves removal of the protecting group, e.g., removal of a carbobenzoxy group, by hydrogenolysis
25 utilizing palladium on carbon in a suitable solvent system such as an alcohol, acetic acid, and the like or mixtures thereof. Where the protecting group is a t-butoxycarbonyl group, it can be removed utilizing an inorganic or organic acid, e.g., HCl or trifluoroacetic acid, in a suitable
30 solvent system, e.g., dioxane or methylene chloride. The resulting product is the amine salt derivative. Following neutralization of the salt, the amine is then reacted with an amino acid or corresponding derivative thereof represented by the formula $(\text{PN}(\text{CR}^1'\text{R}^1'')_t \text{CH}(\text{R}^1)\text{COOH})$
35 wherein t, R¹, R^{1'} and R^{1''} are as defined above, to

produce the antiviral compounds of the present invention having the formula:



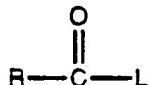
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wherein t , P , R^1 , R^1' , R^1'' , R^2 , R^3 , R^4 and R^5 are as defined above. Preferred protecting groups in this instance are a benzyloxycarbonyl group or a t-butoxycarbonyl group. Where the amine is reacted with a derivative of an amino acid, e.g., when $t=1$ and R^1' and R^1'' are both H, so that the amino acid is a β -amino acid, such β -amino acids can be prepared according to the procedure set forth in a copending application, U. S. Serial No. 07/345,808. Where t is 1, one of R^1' and R^1'' is H and R^1 is hydrogen so that the amino acid is a homo- β -amino acid, such homo- β -amino acids can be prepared by the procedure set forth in a copending application, U.S. Serial No. 07/853,561. Where t is 0 and R^1 is alkyl, alkenyl, alkynyl, cycloalkyl, $-\text{CH}_2\text{SO}_2\text{NH}_2$, $-\text{CH}_2\text{CO}_2\text{CH}_3$, $-\text{CO}_2\text{CH}_3$, $-\text{CONH}_2$, $-\text{CH}_2\text{C(O)NHCH}_3$, $-\text{C}(\text{CH}_3)_2(\text{SH})$, $-\text{C}(\text{CH}_3)_2(\text{SCH}_3)$, $-\text{C}(\text{CH}_3)_2[\text{S(O)CH}_3]$, $-\text{C}(\text{CH}_3)_2[\text{S(O}_2\text{)CH}_3]$, or an amino acid side chain, such materials are well known and many are commercially available from Sigma-Aldrich.

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The N-protecting group can be subsequently removed, if desired, utilizing the procedures described above, and then reacted with a carboxylate represented by the formula:

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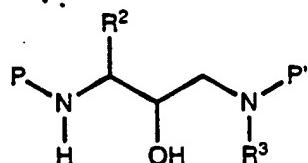


wherein R is as defined above and L is an appropriate leaving group such as a halide. Preferably, where R¹ is a side chain of a naturally occurring α-amino acid, R is a 2-quinoline carbonyl group derived from

- 5 N-hydroxysuccinimide-2-quinoline carboxylate, i.e., L is hydroxy succinimide. A solution of the free amine (or amine acetate salt) and about 1.0 equivalent of the carboxylate are mixed in an appropriate solvent system and optionally treated with up to five equivalents of a base
 10 such as, for example, N-methylmorpholine, at about room temperature. Appropriate solvent systems include tetrahydrofuran, methylene chloride or N,N-dimethylformamide, and the like, including mixtures thereof.

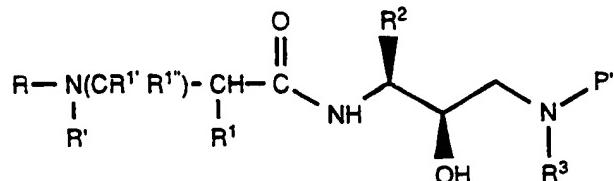
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- Alternatively, the protected amino alcohol from the epoxide opening can be further protected at the newly introduced amino group with a protecting group P' which is not removed when the first protecting P is removed. One skilled in the art can choose appropriate combinations of P and P'. One suitable choice is when P is Cbz and P' is Boc. The resulting compound represented by the formula:



25

can be carried through the remainder of the synthesis to provide a compound of the formula:



and the new protecting group P' is selectively removed, and following deprotection, the resulting amine reacted to form the sulfamic acid derivative as described above. This selective deprotection and conversion to the sulfamic acid can be accomplished at either the end of the synthesis or at any appropriate intermediate step if desired.

It is contemplated that for preparing compounds of the Formulas having R⁶, the compounds can be prepared following the procedure set forth above and, prior to coupling the sulfonamide derivative or analog thereof, e.g. coupling to the amino acid PNH(CH₂)_tCH(R¹)COOH, carried through a procedure referred to in the art as reductive amination. Thus, a sodium cyanoborohydride and an appropriate aldehyde or ketone can be reacted with the sulfonamide derivative compound or appropriate analog at room temperature in order to reductively aminate any of the compounds of Formulas I-IV. It is also contemplated that where R³ of the amino alcohol intermediate is hydrogen, the inhibitor compounds of the present invention wherein R³ is alkyl, or other substituents wherein the α-C contains at least one hydrogen, can be prepared through reductive amination of the final product of the reaction between the amino alcohol and the amine or at any other stage of the synthesis for preparing the inhibitor compounds.

Contemplated equivalents of the general formulas set forth above for the antiviral compounds and derivatives as well as the intermediates are compounds otherwise corresponding thereto and having the same general properties, such as tautomers thereof as well as compounds, wherein one or more of the various R groups are simple variations of the substituents as defined therein, e.g., wherein R is a higher alkyl group than that

indicated. In addition, where a substituent is designated as, or can be, a hydrogen, the exact chemical nature of a substituent which is other than hydrogen at that position, e.g., a hydrocarbyl radical or a halogen, hydroxy, amino 5 and the like functional group, is not critical so long as it does not adversely affect the overall activity and/or synthesis procedure.

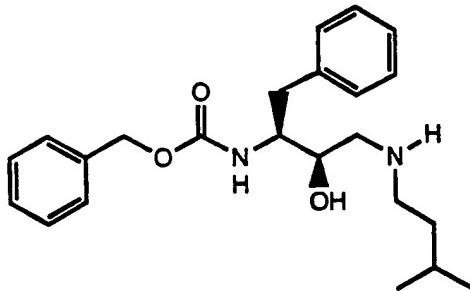
The chemical reactions described above are 10 generally disclosed in terms of their broadest application to the preparation of the compounds of this invention. Occasionally, the reactions may not be applicable as described to each compound included within the disclosed scope. The compounds for which this occurs will be 15 readily recognized by those skilled in the art. In all such cases, either the reactions can be successfully performed by conventional modifications known to those skilled in the art, e.g., by appropriate protection of interfering groups, by changing to alternative 20 conventional reagents, by routine modification of reaction conditions, and the like, or other reactions disclosed herein or otherwise conventional, will be applicable to the preparation of the corresponding compounds of this invention. In all preparative methods, all starting 25 materials are known or readily preparable from known starting materials.

Without further elaboration, it is believed that one skilled in the art can, using the preceding 30 description, utilize the present invention to its fullest extent. The following preferred specific embodiments are, therefore, to be construed as merely illustrative, and not limitative of the remainder of the disclosure in any way whatsoever.

The following Examples 1 through 9 illustrate preparation of intermediates. These intermediates are useful in preparing the inhibitor compounds of the present invention as illustrated in Examples 13-17. In 5 addition, the intermediates of Examples 4-9 are also retroviral protease inhibitors and inhibit, in particular, HIV protease.

Example 1

10



Preparation of N[3(S)-benzyloxycarbonylamo-2(R)-hydroxy-4-phenylbutyl]-N-isoamylamine

15

Part A:

To a solution of 75.0g (0.226 mol) of N-benzyloxycarbonyl-L-phenylalanine chloromethyl ketone in a mixture of 807 mL of methanol and 807 mL of 20 tetrahydrofuran at -2°C, was added 13.17g (0.348 mol, 1.54 equiv.) of solid sodium borohydride over one hundred minutes. The solvents were removed under reduced pressure at 40°C and the residue dissolved in ethyl acetate (approx. 1L). The solution was washed sequentially with 1M potassium hydrogen sulfate, saturated sodium bicarbonate and then saturated sodium chloride solutions. After drying over anhydrous magnesium sulfate and filtering, the solution was removed under reduced pressure. To the resulting oil was added 25 hexane (approx. 1L) and the mixture warmed to 60°C with 30 hexane (approx. 1L) and the mixture warmed to 60°C with

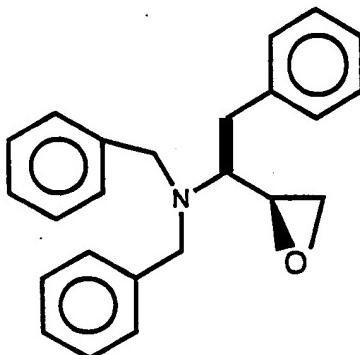
- swirling. After cooling to room temperature, the solids were collected and washed with 2L of hexane. The resulting solid was recrystallized from hot ethyl acetate and hexane to afford 32.3g (43% yield) of
- 5 N-benzyloxycarbonyl-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol, mp 150-151°C and $M+Li^+$ = 340.

Part B:

To a solution of 6.52g (0.116 mol, 1.2 equiv.) of potassium hydroxide in 968 mL of absolute ethanol at room temperature, was added 32.3g (0.097 mol) of N-CBZ-3(S)-amino-1-chloro-4-phenyl-2(S)-butanol. After stirring for fifteen minutes, the solvent was removed under reduced pressure and the solids dissolved in 15 methylene chloride. After washing with water, drying over magnesium sulfate, filtering and stripping, one obtains 27.9g of a white solid. Recrystallization from hot ethyl acetate and hexane afforded 22.3g (77% yield) of N-benzyloxycarbonyl-3(S)-amino-1,2(S)-epoxy-4-phenylbutane, mp 102-103°C and MH^+ 298.

Part C:

A solution of N-benzyloxycarbonyl 3(S)-amino-1,2-(S)-epoxy-4-phenylbutane (1.00g, 3.36 mmol) and 25 isoamylamine (4.90g, 67.2 mmol, 20 equiv.) in 10 mL of isopropyl alcohol was heated to reflux for 1.5 hours. The solution was cooled to room temperature, concentrated in vacuo and then poured into 100 mL of stirring hexane whereupon the product crystallized from solution. The 30 product was isolated by filtration and air dried to give 1.18g, 95% of $N=[(3(S)-phenylmethylcarbamoyl)amino-2(R)-hydroxy-4-phenylbutyl]N-[(3-methylbutyl)]amine$ mp 108.0-109.5°C, MH^+ m/z = 371.

Example 2

5 Preparation of N,N-dibenzyl-3(S)-amino-1,2-(S)-epoxy-4-phenylbutane

Step A:

10 A solution of L-phenylalanine (50.0 g, 0.302 mol), sodium hydroxide (24.2 g, 0.605 mol) and potassium carbonate (83.6 g, 0.605 mol) in water (500 ml) is heated to 97°C. Benzyl bromide (108.5 ml, 0.912 mol) is then slowly added (addition time ~25 min). The mixture is then stirred at 97°C for 30 minutes. The solution is cooled to room temperature and extracted with toluene (2 x 250 ml). The combined organic layers are then washed with water, brine, dried over magnesium sulfate, filtered and concentrated to give an oil product. The crude product is then used in the next step without purification.

Step B:

25 The crude benzylated product of the above step is dissolved in toluene (750 ml) and cooled to -55°C. A 1.5 M solution of DIBAL-H in toluene (443.9 ml, 0.666 mol) is then added at a rate to maintain the temperature between -55° to -50°C (addition time - 1 hour). The

mixture is stirred for 20 minutes at -55°C. The reaction is quenched at -55°C by the slow addition of methanol (37 ml). The cold solution is then poured into cold (5°C) 1.5 N HCl solution (1.8 L). The precipitated solid 5 (approx. 138 g) is filtered off and washed with toluene. The solid material is suspended in a mixture of toluene (400 ml) and water (100 ml). The mixture is cooled to 5°C, treated with 2.5 N NaOH (186 ml) and then stirred at room temperature until the solid is dissolved. The 10 toluene layer is separated from the aqueous phase and washed with water and brine, dried over magnesium sulfate, filtered and concentrated to a volume of 75 ml (89 g). Ethyl acetate (25 ml) and hexane (25 ml) are then added to the residue upon which the alcohol product 15 begins to crystallize. After 30 min., an additional 50 ml hexane is added to promote further crystallization. The solid is filtered off and washed with 50 ml hexane to give approximately 35 g of material. A second crop of material can be isolated by refiltering the mother liquor. 20 The solids are combined and recrystallized from ethyl acetate (20 ml) and hexane (30 ml) to give, in 2 crops, approximately 40 g (40% from L-phenylalanine) of analytically pure alcohol product. The mother liquors are combined and concentrated (34 g). The residue is 25 treated with ethyl acetate and hexane which provides an additional 7 g (~7% yield) of slightly impure solid product. Further optimization in the recovery from the mother liquor is probable.

30 Step C:

A solution of oxalyl chloride (8.4 ml, 0.096 mol) in dichloromethane (240 ml) is cooled to -74°C. A solution of DMSO (12.0 ml, 0.155 mol) in dichloromethane (50 ml) is then slowly added at a rate to maintain the 35 temperature at -74°C (addition time ~1.25 hr). The

mixture is stirred for 5 min. followed by addition of a solution of the alcohol (0.074 mol) in 100 ml of dichloromethane (addition time -20 min., temp. -75°C to -68°C). The solution is stirred at -78°C for 35 minutes.

- 5 Triethylamine (41.2 ml, 0.295 mol) is then added over 10 min. (temp. -78° to -68°C) upon which the ammonium salt precipitated. The cold mixture is stirred for 30 min. and then water (225 ml) is added. The dichloromethane layer is separated from the aqueous phase and washed with
10 water, brine, dried over magnesium sulfate, filtered and concentrated. The residue is diluted with ethyl acetate and hexane and then filtered to further remove the ammonium salt. The filtrate is concentrated to give the desired aldehyde product. The aldehyde was carried on to
15 the next step without purification.

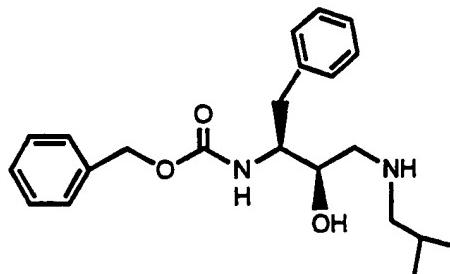
Temperatures higher than -70°C have been reported in the literature for the Swern oxidation. Other Swern modifications and alternatives to the Swern oxidations are also possible.
20

- A solution of the crude aldehyde 0.074 mol and chloroiodomethane (7.0 ml, 0.096 mol) in tetrahydrofuran (285 ml) is cooled to -78°C. A 1.6 M solution of
25 n-butyllithium in hexane (25 ml, 0.040 mol) is then added at a rate to maintain the temperature at -75°C (addition time - 15 min.). After the first addition, additional chloroiodomethane (1.6 ml, 0.022 mol) is added again, followed by n-butyllithium (23 ml, 0.037 mol), keeping
30 the temperature at -75°C. The mixture is stirred for 15 min. Each of the reagents, chloroiodomethane (0.70 ml, 0.010 mol) and n-butyllithium (5 ml, 0.008 mol) are added 4 more times over 45 min. at -75°C. The cooling bath is then removed and the solution warmed to 22°C over 1.5 hr.
35 The mixture is poured into 300 ml of saturated aq.

ammonium chloride solution. The tetrahydrofuran layer is separated. The aqueous phase is extracted with ethyl acetate (1 x 300 ml). The combined organic layers are washed with brine, dried over magnesium sulfate, filtered and concentrated to give a brown oil (27.4 g). The product could be used in the next step without purification. The desired diastereomer can be purified by recrystallization at a subsequent step.

10 Alternately, the product could be purified by chromatography.

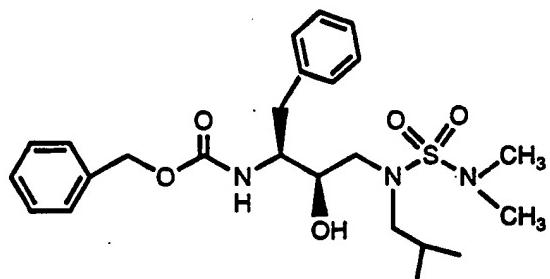
Example 3



15

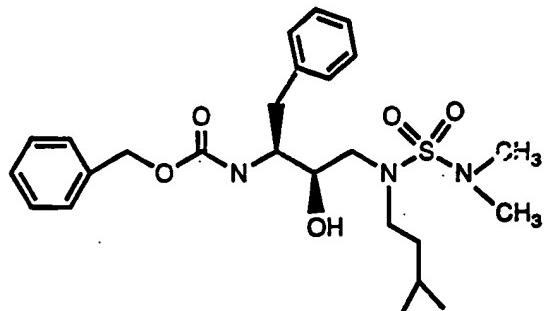
Preparation of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenyl]N-isobutylamine

20 A solution of N-benzyloxycarbonyl-3(S)-amino-1,2-(S)-epoxy-4-phenyl butane (50.0 g, 0.168 mol) and isobutylamine (246 g, 3.24 mol, 20 equivalents) in 650 mL of isopropyl alcohol was heated to reflux for 1.25 hours. The solution was cooled to room temperature, concentrated 25 in vacuo and then poured into 1 L of stirring hexane whereupon the product crystallized from solution. The product was isolated by filtration and air dried to give 57.56 g, 92% of N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenyl]N-isobutylamine, mp 108.0-109.5 °C, MH+ 30 m/z=371.

Example 4

5 Preparation of phenylmethyl[2R-hydroxy-3-[(dimethylamino)sulfonyl](2-methylpropyl)aminol-1S-(phenylmethyl)propyl]carbamate

The product from Example 3 (740 mg, 2.0 mmol) and
10 diisopropylethylamine (382 uL, 2.2 mmol) were dissolved in
dichloromethane (1.5 mL) at room temperature. To this was
added dimethylsulfamoyl chloride (354 uL, 3.3 mmol). The
reaction was stirred for 24 hours. The reaction mixture was
chromatographed on silica gel (50 gm) using 1% ethanol in
15 chloroform. The product fractions were pooled and
concentrated to an oil. Anal. Calcd for C₂₄H₃₅N₃O₅S:
C, 60.35; H, 7.39; N, 8.80. Found: C, 60.18; H, 7.40;
N, 8.55.

Example 5

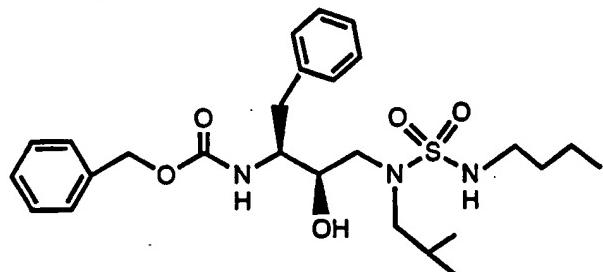
- 5 Preparation of phenylmethyl[2R-hydroxy-3-[(dimethylamino)sulfonyl](3-methylbutyl)aminol-1S-(phenylmethyl)propyl]carbamate

Part A

10 The procedure described in Example 1 was used to prepare N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]-N-[(3-methylbutyl)]amine.

Part B

15 The product from Part A (192 mg, 0.5 mmol) and diisopropylethylamine (96 uL, 0.55 mmol) were dissolved in dichloromethane (10 mL) at room temperature. To this was added dimethylsulfamoyl chloride (59 uL, 0.55 mmol). The reaction was stirred for 120 hours, then concentrated on a
20 rotary evaporator. The residue was chromatographed on silica gel (50 gm) using 2% methanol in dichloromethane. The product fractions were pooled and concentrated to an oil which solidified on standing. Anal. Calcd for C₂₅H₃₇N₃O₅S. 0.9 H₂O: C, 59.13; H, 7.64; N, 8.27; S, 6.31. Found:
25 C, 58.81; H, 7.38; N, 8.62; S, 6.70.

Example 6

- 5 Preparation of phenylmethyl [3-[1-(butylamino)sulfonyl](2-methylpropyl)aminol-2R-hydroxy-1S-(phenylmethyl)propyl]carbamate

Part A:

10

To a stirred solution of 3.88 gm (2 mL) of 30% fuming sulfuric acid in nitromethane (10mL) was added dropwise n-butyliisocyanate (3.83 mL, 34 mmoles) at 0 C. After the addition was completed, the suspension was heated 15 in an oil bath at 120 C. for 30 min. The reaction was cooled and filtered. The collected sulfamic acid crystals were air dried, wt. 4.73 gm (91%).

Part B:

20

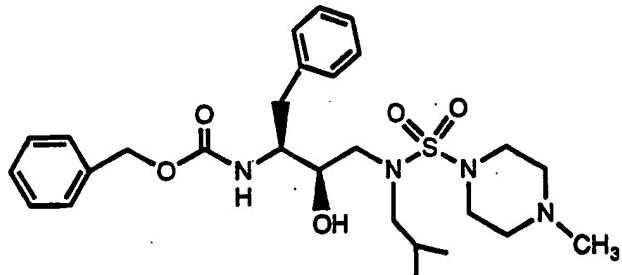
A suspension of n-butyl sulfamic acid (1.92 gm, 12.53 mmoles) and phosphorus pentachloride (2.61 gm, 12.53 mmoles) in benzene (20 mL) was warmed gently to initiate gas evolution. The reaction mixture was stirred at room 25 temperature for 0.5 h., during which time a cloudy solution resulted. The cloudy solution was heated to reflux for 0.5 h., then was concentrated. The product n-butyl sulfamoyl chloride was isolated by vacuum distillation (120 C., 300 millitorr), 730 mg (liq.) (34%).

30

Part C:

The amine alcohol from Example 3 (370 mg, 1 mmole) was dissolved in 3 mL of dichloromethane and treated
5 with diisopropylethylamine (278 uL, 2 mmoles), followed by chlorotrimethylsilane (126 uL, 1 mmole). The reaction mixture was stirred at r.t. for 1 h. n-Butyl sulfamoyl chloride from Part B (171 mg, 1 mmole) was added and the mixture was stirred at r.t. overnight. After removal of
10 dichloromethane the oily residue was taken up in ethyl acetate and washed successively with 5% citric acid, saturated sodium bicarbonate, brine, dried over sodium sulfate and the solvent was evaporated to give 512 mg of product (oil).

15 The oily product (510 mg) was dissolved in dichloromethane (3 mL) and was treated with 2 mL of 4N HCl in dioxane. After 15 min. methanol (5 mL) was added and the solution was stirred for an additional 15 min. Solvent and
20 excess reagent were evaporated. The product was isolated by silica gel chromatography to give 357 mg of phenylmethyl [3-[(butylamino)sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl carbamate. Anal. Calcd for C₂₆H₃₉N₃O₅S: C, 61.76; H, 7.77; N, 8.31. Found: C, 61.89;
25 H, 7.66; N, 8.18.

Example 7

5 Preparation of phenylmethyl [2R-hydroxy-3-[(4-methyl-1-piperazinyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl carbamate

Part A:

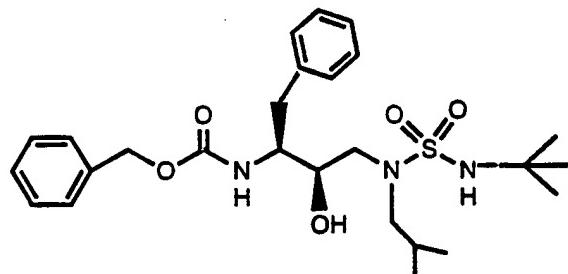
10 1-methylpiperazine hydrochloride (3.46 gm, 20 mmoles) was added in portions within 15 min. to a stirred solution of sulfonyl chloride (8.99 gm, 67 mmoles) in acetonitrile(40 mL). The suspension was gradually warmed to 15 reflux and maintained at reflux temperature overnight. A brown solution was obtained. After cooling to r.t., the crystals were collected by filtration, wt. 2.3 gm. A sample of 4-methyl-1-piperazine sulfamoyl chloride.HCl was recrystallized from methanol. Anal. Calcd. for
15 C₅H₁₂N₂O₂Cl₂S: C, 25.54; H, 5.14; N, 11.91; Cl, 30.16.
20 Found: C, 25.54; H, 4.91; N, 11.91; Cl, 29.88.

Part B:

25 N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]-N-isobutylamine (370 mg, 1.0 mmole), prepared according to the procedure in Example 3 was mixed with DIEA (280 uL, 2.0 mmoles) and 4-methyl-1-piperazine sulfamoyl chloride.HCl (240 mg, 1.0 mmole) in 6 mL of dichloromethane.
30 The reaction mixture was stirred for 5 days. After

filtration, the filtrate was concentrated to an oil, which was taken up in ethyl acetate. The ethyl acetate solution was washed with sodium bicarbonate solution, brine and dried over sodium sulfate. After evaporation, phenylmethyl [2R-hydroxy-3-[(4-methyl-1-piperazinyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl carbamate was obtained (412 mg).

10

Example 8

Preparation of phenylmethyl [2R-hydroxy-3-[(4-methyl-1-dimethylaminol)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl carbamate

Part A:

20 A 25 mL two-necked RB flask, equipped with a reflux condenser and dropping funnel and under a nitrogen atmosphere, was charged with t-butanol (207 uL, 2.2 mmoles) and 5 mL of hexane. Chlorosulfonyl isocyanate (192 uL, 2.2 mmoles) in 3 mL of hexane was added dropwise. Upon warming a homogeneous solution was obtained. The solution was heated at gentle reflux for 45 min., then was cooled to r.t. Solvent was removed under a steady stream of nitrogen. The crude t-butyl sulfamoyl chloride (a liquid) was used without further purification.

Part B:

N[3(S)-benzyloxycarbonylamino-2(R)-hydroxy-4-phenylbutyl]-N-isobutylamine (370 mg, 1.0 mmole), prepared according to the procedure in Example 3 was mixed with DIEA (139 uL, 1 mmole) in 5 mL of dichloromethane. Chlorotrimethylsilane (126 uL, 1 mmole) was added. After 1 h., additional DIEA (160 uL) was added, followed by a dichloromethane solution (5mL) containing 1.1 mmole of t-butyl sulfamoyl chloride from Part A. The reaction mixture was stirred for 2 days. Solvent was removed under aspirator pressure. The oily residue was taken up in ethyl acetate and washed with 5% citric acid, saturated sodium bicarbonate, brine, dried over sodium sulfate and evaporated to an oily residue (380 mg).

The crude product was stirred in 4N HCl in dioxane (6 mL) for 15 min. After the addition of 4 mL of methanol to the reaction mixture, the solution was stirred for an additional 15 min, then concentrate to an oily residue. The product, phenylmethyl [2R-hydroxy -3-[(1,1-dimethylethyl)amino]sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl carbamate was obtained after silica gel chromatography (188 mg, 37%). MS (MH)⁺ = 506.

25

Example 9

Preparation of phenylmethyl [2R-hydroxy-3-[(piperidyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propylcarbamate

Part A:

The product of Example 3 (750 mg. 2.02 mmol) and triethylamine (280 uL, 2.02 mmol) were dissolved in

dichloromethane (8.0 mL) at room temperature. To this was added piperidinesulfamoyl chloride (371 mg, 2.02 mmol). The reaction was stirred for 72 hours and then concentrated. 5 The residue was chromatographed on silica gel (50 gm) using 5% methanol in dichloromethane. The product fractions were pooled and concentrated to an oil, 945 mg. TLC (silica / 5% MeOH in CH₂Cl₂) showed two spots. Rechromatographed. Anal. Calcd for C₂₇H₃₉N₃O₅S: C, 62.63; H, 7.51; N, 8.06. Found: C, 62.64; H, 7.59; N, 8.12.

10

Part B:

The product of Part A (430 mg) was combined with 10% Pd/C in methanol (10 mL) and hydrogenated at 5 psi for 15 1.4 hours at room temperature. The catalyst was removed by filtration and the solvent evaporated to afford the product as an oil, 305 mg.

Part C:

20

To a solution of Cbz-L-t-leucine (236 mg, 0.89 mmol) in DMF (2 mL) was added HOBr (115 mg, 0.85 mmol) and EDC (163 mg, 0.85 mmol). The reaction was stirred at room temperature for 1 hour and then a solution of the product 25 from part B (305 mg, 0.79 mmol) in DMF (2 mL) was added. The reaction was stirred for 18 hours then concentrated. The residue was taken up in ethyl acetate and washed with 0.5% HCl solution, saturated aqueous NaHCO₃, and saturated aqueous NaCl (50 mL each). The organic solution was dried 30 (Na₂SO₄), filtered and concentrated to a foam, 410 mg. ¹H NMR supports product.

Part D:

The product of Part C (410 mg) was combined with 10% Pd/C in methanol (10 mL) and hydrogenated at 5 psi for 5 2.0 hours at room temperature. The catalyst was removed by filtration and the solvent evaporated to afford the product as an foam, 320 mg.

Part E:

10 To a solution of the product of Part D (310 mg, 0.62 mmol) in dichloromethane (10 mL) was added diisopropylethylamine (130 uL, 0.75 mmol) and chloroacetic anhydride (117 mg, 0.68 mmol) at 0 C. The reaction was 15 allowed to warm to room temperature and stir one hour. The solvent was removed and the residue taken up in ethyl acetate (50 mL). The organic solution was washed with 5% citric acid, saturated NaHCO₃, and saturated NaCl (50 mL each). The solution was dried (Na₂SO₄), filtered and 20 concentrated to give a solid, 350 mg.

Part F:

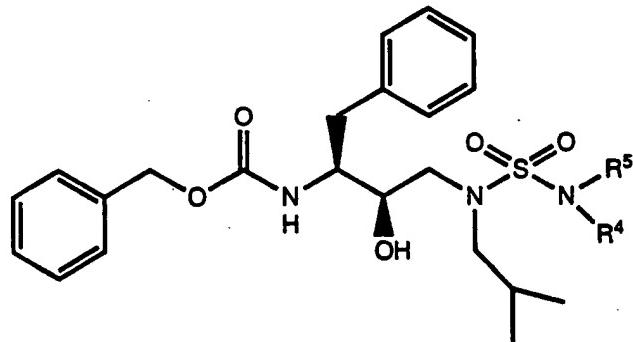
The product of Part E (350 mg, 0.61 mmol) was 25 combined with 40% aqueous dimethylamine (280 uL, 3.05 mmol) in isopropanol (10 mL). The reaction was stirred for 18 hours then concentrated. The residue was taken up in ethyl acetate (50 mL) and washed with water, saturated NaHCO₃, and saturated NaCl (50 mL each). The solution was dried 30 (Na₂SO₄), filtered and concentrated to a solid. The solid was chromatographed on silica gel using 2% MeOH in dichloromethane. The product fractions were pooled and concentrated to give a white solid. Anal. Calcd for C₂₉H₅₁N₅O₅S. 0.25 H₂O: C, 59.41; H, 8.77; N, 11.94. Found: 35 C, 59.35; H, 8.78; N, 11.63.

Example 10

Following the procedures of the previous Examples 1-9, the intermediate compounds set forth in
5 Tables 1A, 1B and 1C were prepared.

TABLE 1A

10	R ³	R ⁴
		R ⁵
	isobutyl	CH ₃
	isoamyl	CH ₃
	isobutyl	CH ₂ CH ₂ CH ₂ CH ₃
15	isobutyl	C(CH ₃) ₃
		H

TABLE 1B

5

	<u>Entry</u>	<u>R⁴</u>	<u>R⁵</u>
	1	CH ₃	CH ₃
	2	H	CH ₃
10	3	H	(CH ₂) ₃ CH ₃
	4	H	CH(CH ₃) ₂
	5	H	C(CH ₃) ₃
	6	H	cyclohexyl
	7	$\text{R}^4 \text{ & } \text{R}^5 = \text{pyrrolidinyl}$	

TABLE 1C

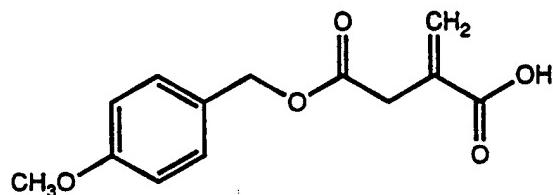
Entry	R ³	R ⁴	R ⁵
5	A isobutyl	methyl	H
	B p-fluorobenzyl	methyl	methyl
10	C isobutyl	isopropyl	H
	D isobutyl	NR ⁴ R ⁵ =	
15	E isobutyl	phenyl	H
	F isobutyl	NR ⁴ R ⁵ =	
20	G isobutyl	NR ⁴ R ⁵ =	
	H benzyl	t-butyl	H
25	I cyclohexylmethyl	t-butyl	H
	J isobutyl	C(CH ₃) ₂ CO ₂ Me	H
30	K cyclohexyl	t-butyl	H
	L isobutyl	(CH ₂) ₂ OCH ₂ C ₆ H ₅	H
	M isobutyl	cyclohexyl	H

The following Examples 11-13 illustrate preparation of β -amino acid intermediates. These intermediates can be coupled to the intermediate compounds of Examples 1-10 to produce inhibitor compounds 5 of the present invention containing β -amino acids.

Example 11

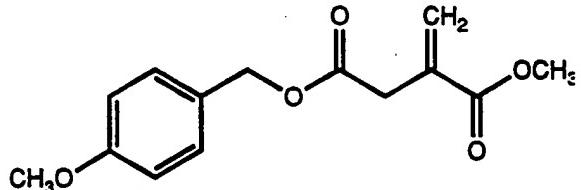
A. Preparation of 4(4-methoxybenzyl)itaconate

10



A 5 L three-necked round bottomed flask equipped with constant pressure addition funnel, reflux 15 condenser, nitrogen inlet, and mechanical stirrer was charged with itaconic anhydride (660.8g, 5.88 mol) and toluene (2300 mL). The solution was warmed to reflux and treated with 4-methoxybenzyl alcohol (812.4g, 5.88 mol) dropwise over a 2.6h period. The solution was maintained 20 at reflux for an additional 1.5h and then the contents were poured into three 2 L erlenmeyer flasks to crystallize. The solution was allowed to cool to room temperature whereupon the desired mono-ester 25 crystallized. The product was isolated by filtration on a Buchner funnel and air dried to give 850.2g, 58% of material with mp 83-85°C, a second crop, 17% was isolated after cooling of the filtrate in an ice bath. ^1H NMR (CDCl₃) 300 MHz 7.32(d, J=8.7 Hz, 2H), 6.91(d, J=8.7 Hz, 2H), 6.49(s, 1H), 5.85(s, 1H), 5.12(s, 2H), 3.83(s, 3H), 30 3.40(s, 2H).

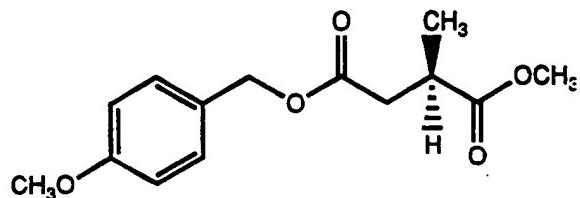
B. Preparation of Methyl 4(4-methoxybenzyl) itaconate



5 A 5 L three-necked round bottomed flask equipped with reflux condenser, nitrogen inlet, constant pressure addition funnel and mechanical stirrer was charged with 4(4-methoxybenzyl) itaconate (453.4g, 1.81 mol) and treated with 1,5-diazabicyclo[4.3.0]non-5-ene (275.6g, 1.81 mol), (DBN), dropwise so that the temperature did not rise above 15°C. To this stirring mixture was added a solution of methyl iodide (256.9g, 1.81 mol) in 250 mL of toluene from the dropping funnel over a 45m period. The solution was allowed to warm to room temperature and stirred for an additional 3.25h.

10 The precipitated DBN hydroiodide was removed by filtration, washed with toluene and the filtrate poured into a separatory funnel. The solution was washed with sat. aq. NaHCO₃ (2 X 500 mL), 0.2N HCl (1 X 500 mL), and brine (2 X 500 mL), dried over anhyd. MgSO₄, filtered, and the solvent removed in vacuo. This gave a clear colorless oil, 450.2g, 94% whose NMR was consistent with the assigned structure. ¹H NMR (CDCl₃) 300 MHz 7.30(d, J=8.7 Hz, 2H), 6.90(d, J=8.7 Hz, 2H), 6.34(s, 1H), 5.71(s, 1H), 5.09(s, 2H), 3.82(s, 3H), 3.73(s, 3H), 3.38(s, 2H). ¹³C NMR (CDCl₃) 170.46, 166.47, 159.51, 133.55, 129.97, 128.45, 127.72, 113.77, 66.36, 55.12, 51.94, 37.64.

C. Preparation of Methyl 4(4-methoxybenzyl) 2(R)-methylsuccinate



5

A 500 mL Fisher-Porter bottle was charged with methyl 4(4-methoxybenzyl) itaconate (71.1g, 0.269 mol), rhodium (R,R) DiPAMP catalyst (204mg, 0.269 mmol, 0.1 mol%) and degassed methanol (215 mL). The bottle was flushed 5 times with nitrogen and 5 times with hydrogen to a final pressure of 40 psig. The hydrogenation commenced immediately and after ca. 1h the uptake began to taper off, after 3h the hydrogen uptake ceased and the bottle was flushed with nitrogen, opened and the contents concentrated on a rotary evaporator to give a brown oil that was taken up in boiling iso-octane (ca. 200 mL, this was repeated twice), filtered through a pad of celite and the filtrate concentrated *in vacuo* to give 66.6g, 93% of a clear colorless oil, ^1H NMR (CDCl_3 300 MHz 7.30(d, 5H, $J=8.7$ Hz, 2H), 6.91(d, $J=8.7$ Hz, 2H), 5.08(s, 2H), 3.82(s, 3H), 3.67(s, 3H), 2.95(ddq, $J=5.7, 7.5, 8.7$ Hz, 1H), 2.79(dd, $J=8.1, 16.5$ Hz, 1H), 2.45(dd, $J=5.7, 16.5$ Hz, 1H), 1.23(d, $J=7.5$ Hz, 3H).

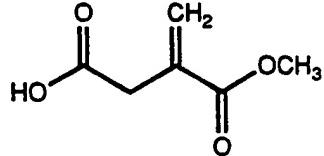
25 D. Preparation of Methyl 2(R)-methylsuccinate

A 3 L three-necked round-bottomed flask equipped with a nitrogen inlet, mechanical stirrer, reflux condenser and constant pressure addition funnel was charged with methyl 4(4-methoxybenzyl) 2(R)-methylsuccinate (432.6g, 1.65 mol) and toluene (1200 mL). The stirrer was started and the solution treated with trifluoroacetic acid (600 mL) from the dropping funnel

over 0.25h. The solution turned a deep purple color and the internal temperature rose to 45°C. After stirring for 2.25h the temperature was 27°C and the solution had acquired a pink color. The solution was concentrated on 5 a rotary evaporator. The residue was diluted with water (2200 mL) and sat. aq. NaHCO₃ (1000 mL). Additional NaHCO₃ was added until the acid had been neutralized. The aqueous phase was extracted with ethyl acetate (2 X 1000 mL) to remove the by-products and the aqueous layer 10 was acidified to pH=1.8 with conc. HCl. This solution was extracted with ethyl acetate (4 X 1000 mL), washed with brine, dried over anhyd. MgSO₄, filtered and concentrated on a rotary evaporator to give a colorless liquid 251g, >100% that was vacuum distilled through a 15 short path apparatus cut 1: bath temperature 120°C @ >1mm, bp 25-29°C; cut 2: bath temperature 140°C @ 0.5mm, bp 95-108°C, 151g, $[\alpha]_d$ @ 25°C = +1.38°C (c=15.475, MeOH), $[\alpha]_d$ = +8.48°C (neat); cut 3: bath temperature 140°C, bp 108°C, 36g, $[\alpha]_d$ @ 25°C = +1.49°C (c=15.00, MeOH), $[\alpha]_d$ 20 = +8.98°C (neat). Cuts 2 and 3 were combined to give 189g, 78% of product, ¹H NMR (CDCl₃) 300 MHz 11.6(brs, 1H), 3.72(s, 3H), 2.92(ddq, J=5.7, 6.9, 8.0 Hz, 1H), 2.81(dd, J=8.0, 16.8 Hz, 1H), 2.47(dd, J=5.7, 16.8 Hz, 1H), 1.26(d, J=6.9 Hz, 3H).

25

E. Preparation of Methyl Itaconate



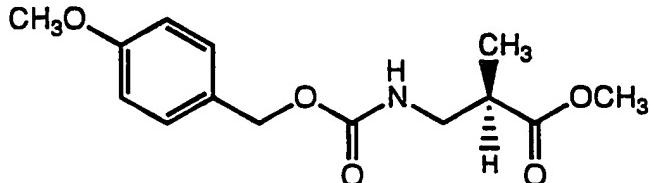
30 A 50 mL round bottomed flask equipped with reflux condenser, nitrogen inlet and magnetic stir bar was charged with methyl 4(4-methoxybenzyl) itaconate (4.00g, 16 mmol), 12 mL of toluene and 6 mL of trifluoroacetic acid. The solution was kept at room

temperature for 18 hours and then the volatiles were removed in vacuo. The residue was taken up in ethyl acetate and extracted three times with saturated aqueous sodium bicarbonate solution. The combined aqueous 5 extract was acidified to pH=1 with aqueous potassium bisulfate and then extracted three times with ethyl acetate. The combined ethyl acetate solution was washed with saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate, filtered, and concentrated 10 in vacuo. The residue was then vacuum distilled to give 1.23g, 75% of pure product, bp 85-87 @ 0.1 mm. ¹H NMR (CDCl₃) 300 MHz 6.34(s, 1H), 5.73(s, 2H), 3.76(s, 3H), 3.38(s, 2H). ¹³C NMR (CDCl₃) 177.03, 166.65, 129.220, 132.99, 52.27, 37.46.

15

F. Curtius Rearrangement of Methyl 2(R)-methylsuccinate:
Preparation of Methyl N-Moz- α -methyl β -alanine.

20



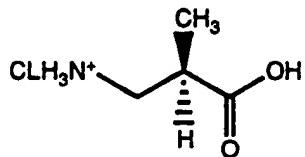
25

A 5L four necked round bottomed flask equipped with a nitrogen inlet, reflux condenser, mechanical stirrer, constant pressure addition funnel, and thermometer adapter was charged with methyl 2(R)-methylsuccinate (184.1g, 1.26 mol), triethylamine (165.6g, 218 mL, 1.64 mol, 1.3 equivalents), and toluene (1063 mL). The solution was warmed to 85°C and then treated dropwise with a solution of diphenylphosphoryl 30 azide (346.8g, 1.26 mol) over a period of 1.2h. The solution was maintained at that temperature for an additional 1.0h and then the mixture was treated with 4-methoxybenzyl alcohol (174.1g, 1.26 mol) over a 0.33h

- period from the dropping funnel. The solution was stirred at 88°C for an additional 2.25h and then cooled to room temperature. The contents of the flask were poured into a separatory funnel and washed with sat. aq.
- 5 NaHCO₃ (2 X 500 mL), 0.2N HCl (2 X 500 mL), brine (1 X 500 mL), dried over anhyd. MgSO₄, filtered, and concentrated in vacuo to give 302.3g, 85% of the desired product as a slightly brown oil. ¹H NMR (CDCl₃) 300 MHz 7.32(d, J=8.4 Hz, 2H), 6.91(d, J=8.4 Hz, 2H), 5.2(brm, 1H), 5.05(s, 2H), 3.83(s, 3H), 3.70(s, 3H), 3.35(m, 2H), 2.70(m, 2H), 1.20(d, J=7.2 Hz, 3H).

G. Hydrolysis of Methyl N-Moz- α -methyl β -alanine:
Preparation of α -methyl β -alanine Hydrochloride

15

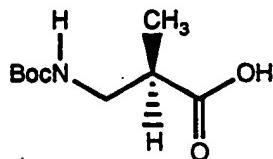


- A 5 L three-necked round bottomed flask equipped with a reflux condenser, nitrogen inlet and mechanical stirrer was charged with methyl N-Moz- α -methyl β -alanine (218.6g, 0.78 mol), glacial acetic acid (975 mL) and 12N hydrochloric acid (1960 mL). The solution was then heated to reflux for 3h. After the solution had cooled to room temperature (ca. 1h) the aqueous phase was decanted from organic residue (polymer) and the aqueous phase concentrated on a rotary evaporator. Upon addition of acetone to the concentrated residue a slightly yellow solid formed that was slurried with acetone and the white solid was isolated by filtration on a Buchner funnel.
- 20 The last traces of acetone were removed by evacuation to give 97.7g, 90% of pure product, mp 128.5-130.5°C [α]_D @ 25°C=9.0°C (c=2.535, Methanol). ¹H NMR (D₂O) 300 MHz 3.29(dd, J=8.6, 13.0 Hz, 1H), 3.16(dd, J=5.0, 13.0 Hz,

1H), 2.94(ddq, $J=7.2, 5.0, 8.6$ Hz, 1H), 1.30(d, $J=7.2$ Hz, 3H); ^{13}C NMR (D_2O) 180.84, 44.56, 40.27, 17.49.

H. Preparation of N-Boc α -Methyl β -Alanine

5



A solution of α -methyl β -alanine hydrochloride (97.7g, 0.70 mol) in water (1050 mL) and dioxane (1050 mL) the pH was adjusted to 8.9 with 2.9N NaOH solution. This stirring solution was then treated with di-*tert*-butyl pyrocarbonate (183.3g, 0.84 mol, 1.2 equivalents) all at once. The pH of the solution was maintained between 8.7 and 9.0 by the periodic addition of 2.5N NaOH solution. After 2.5h the pH had stabilized and the reaction was judged to be complete. The solution was concentrated on a rotary evaporator (the temperature was maintained at <40°C). The excess di-*tert*-butyl pyrocarbonate was removed by extraction with dichloromethane and then the aqueous solution was acidified with cold 1N HCl and immediately extracted with ethyl acetate (4 X 1000 mL). The combined ethyl acetate extract was washed with brine, dried over anhyd. MgSO_4 , filtered and concentrated on a rotary evaporator to give a thick oil 127.3g, 90% crude yield that was stirred with n-hexane whereupon crystals of pure product formed, 95.65g, 67%, mp 76-78°C, $[\alpha]_d^0$ 25°C = -11.8°C (c=2.4, EtOH). A second crop was obtained by concentration of the filtrate and dilution with hexane, 15.4g, for a combined yield of 111.05g, 78%. ^1H NMR (acetone D₆) 300 MHz 11.7 (brs, 1H), 6.05 (brs 1H), 3.35 (m, 1H), 3.22 (m, 1H), 2.50 (m, 1H), 1.45(s, 9H), 1.19 (d, $J=7.3$ Hz, 3H); ^{13}C NMR (acetone D₆) 177.01, 79.28, 44.44, 40.92, 29.08, 15.50. Elemental analysis calc'd. for C₉H₁₇NO₄:

C, 53.19, H, 8.42; N, 6.89. Found: C, 53.36; H, 8.46; N, 6.99.

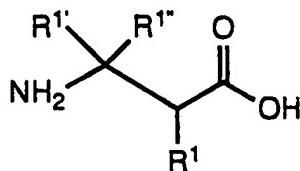
I. Preparation of N-4-Methoxybenzyloxycarbonyl α -Methyl
5 β -Alanine

A solution of N-4-methoxybenzyloxycarbonyl α -methyl β -alanine methyl ester (2.81g, 10.0 mmol) in 30 mL of 25% aqueous methanol was treated with lithium 10 hydroxide (1.3 equivalents) at room temperature for a period of 2h. The solution was concentrated in vacuo and the residue taken up in a mixture of water and ether and the phases separated and the organic phase discarded. The aqueous phase was acidified with aqueous potassium 15 hydrogen sulfate to pH=1.5 and then extracted three times with ether. The combined ethereal phase was washed with saturated aqueous sodium chloride solution, dried over anhydrous magnesium sulfate, filtered and concentrated in vacuo to give 2.60 g, 97% of N-4-Methoxybenzyloxycarbonyl 20 α -methyl β -alanine (N-Moz-AMBA) which was purified by recrystallization from a mixture of ethyl acetate and hexane to give 2.44g, 91% of pure product, mp 96-97°C, MH⁺=268. ¹H NMR (D₆-acetone/300 MHz) 1.16 (3H, d, J=7.2Hz), 2.70 (1H, m), 3.31 (2H, m), 3.31 (3H, s), 4.99 25 (2H, s), 6.92 (2H, 4, J=8.7 Hz), 7.13 (2H, d, J=8.7 Hz).

Example 12

Following generally the procedure of Example 11, the β -amino acids set forth in Table 2 were prepared.

5

Table 2

10

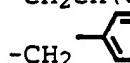
Entry	R ¹	R ^{1'}	R ^{1''}
15	-CH ₃	H	H
	-CH(CH ₃) ₂	H	H
	-C(CH ₃) ₃	H	H
	H	H	H
	H	-CH ₃	H
	H	-CH ₃	-CH ₃
20	H	H	-CO ₂ CH ₃
	H	H	-CONH ₂
	-CH ₂ CH ₃	H	H
	-CH ₂ CH(CH ₃) ₂	H	H
	-CH ₂ C ₆ H ₅	H	H
	25	-CH ₂ -  -OH	H
		-CH ₂ - 	H
		-CH ₂ COOH	H
		H	-CH(CH ₃) ₂
30	16	H	-CH ₂ CH(CH ₃) ₂
		H	-CH ₂ - 

Table 2 (Cont'd)

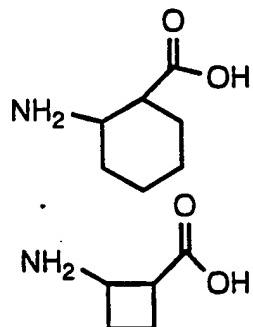
Entry	R ¹	R ^{1'}	R ^{1"}
5			
18	H	-CH ₂ CH ₂ - 	H
19	H	- (CH ₂) ₃ - 	H
20	H	- (CH ₂) ₄ - 	H
21	H	- (CH ₂) ₃ CH(C ₆ H ₅) ₂	H

10

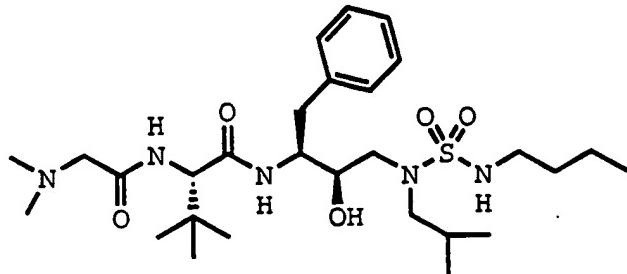
Example 13

15

Utilizing generally the procedure set forth in Example 11, the following β -amino acid compounds were prepared.



20

Example 14

5 Preparation of N-[3-[(butylamino)sulfonyl](2-
methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl-
2S-[2-(dimethylamino)-1-
oxoethyl]aminodimethylbutanamide

10 Part A:

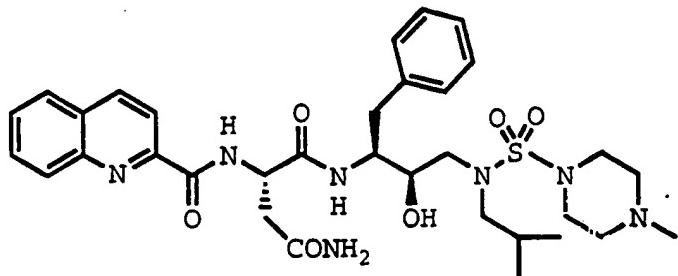
The product from Example 3 (357 mg, 0.71 mmol) in 10 mL of methanol was hydrogenated over 10% palladium on carbon (60 mg) for 5 hr. The mixture was then
15 filtered through Celite and concentrated to give the product as an oil (213 mg).

Part B:

20 The free amine from Part A (210 mg, 0.566 mmol) was coupled with N-CBZ-L-t-butylglycine (180 mg, 0.679 mmol) in the presence of N-hydroxybenzotriazole (92 mg, 0.679 mmol) and EDC (130 mg, 0.679 mmol) to yield 275 mg of phenylmethyl [[[1S-[3-[(butylamino)sulfonyl](2-
25 methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-amino]carbonyl]-2,2-dimethylpropyl]carbamate after purification on silica column.

Part C:

The product from Part B (235 mg) in methanol was hydrogenated over 10% palladium on carbon (50 mg) for 5 4 h. The mixture was filtered through Celite and concentrated to give the product as an oil (173 mg, 0.369 mmol). This free amine was then dissolved in 3 mL of dichloromethane and acylated with bromo acetyl chloride (34 uL, 0.406 mmol) in the presence of DIEA (62 uL, 0.443 mmol) for 2 h. The crude mixture (190 mg, 0.32 mmol) was dissolved in 1 mL of isopropanol and mixed with a 40% wt dimethylamine in water (180 uL, 1.6 mmol) and stirred overnight. Solvent and excess reagents were evaporated. The oily residue was taken up in ethylacetate, washed 10 with saturated sodium bicarbonate, brine and dried over sodium sulfate. The product N-[3-[[[(butylamino)-15 sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[[2-(dimethylamino)-1-oxoethyl]amino]3,3-dimethylbutanamide was purified by 20 silica gel chromatography. Anal. Calc'd for C₂₈H₅₁N₅O₅S. 0.5 H₂O: C, 58.10; H, 9.06; N, 12.09. Found: C, 57.81; H, 8.44; N, 12.01. EI MS M⁺ = 569.

Example 15

5 Preparation of N1-[2R-hydroxy-3-[(4-methyl-1-
piperazinyl)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl-2S-[(2-
quinolinylcarbonyl)amino]butanediamide

10 Part A:

A solution of the carbamate from Example 7 (412 mg, 0.77 mmoles) containing 20 mL methanol and 5 mL acetic acid was hydrogenated over 10% palladium on carbon 15 (80 mg) for 6 h. After filtration of the reaction mixture, the filtrate was evaporated to an oil. The oily residue was dissolved in ethyl acetate and washed with sodium bicarbonate solution. The organic layer was evaporated to give the free amine (100 mg).

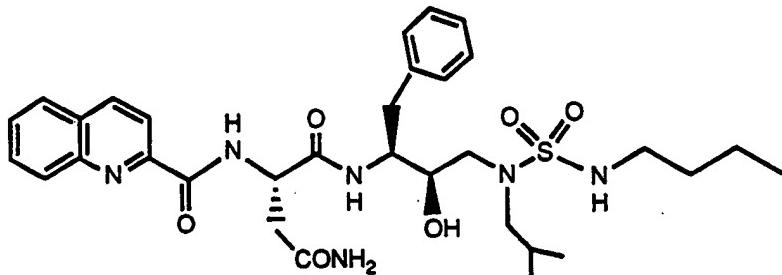
20

Part B:

The free amine from Part A (80 mg, 0.20 mmoles) was coupled with N-BOC-L-asparagine (61 mg, 0.264 mmoles) 25 in the presence of N-hydroxybenzotriazole (48mg, 0.35 mmoles) and EDC (50 mg, 0.264 mmoles) to yield 125 mg of N1[2R-hydroxy -3-[(4-methyl-1-piperazinyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2S-[(1,1-dimethylethoxycarbonyl)amino]butane diamide.

Part C:

N1[2R-hydroxy -3-[3-[(4-methyl-1-piperaziny)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]]-2S-[(1,1-dimethylethoxycarbonyl)amino]butane diamide (118 mg, 0.19 mmole) was stirred in 4N HCl in dioxane (5 mL) at r.t. for 0.5 h. Solvent and excess reagent were evaporated to dryness. The product was dried in vacuo. This material (116 mg, 0.19 mmoles) was then reacted with 2-quinoline carboxylic acid N-hydroxysuccimide ester (53 mg, 0.19 mmoles), DIEA (83 uL, 0.60 mmoles) in DMF (1 mL) overnight. The product N1-[2R-hydroxy -3-[(4-methyl-1-piperaziny)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamid was purified by silica gel chromatography. Anal. Calcd for C₃₃H₄₅N₇O₆S. 0.5 H₂O/0.3 CH₃CH₂OCH₂CH₃: C, 58.76; H, 7.06; N, 14.03. Found: C, 58.23; H, 6.98; N, 13.81.

Example 16

5 Preparation of N1-[3-[1-(butylamino)sulfonyl](2-
methylpropyl)amino]-2R-hydroxy-1S-
(phenylmethyl)propyl-2S-[1-(2-
quinolinylcarbonyl)aminobutanediamicide

10 Part A:

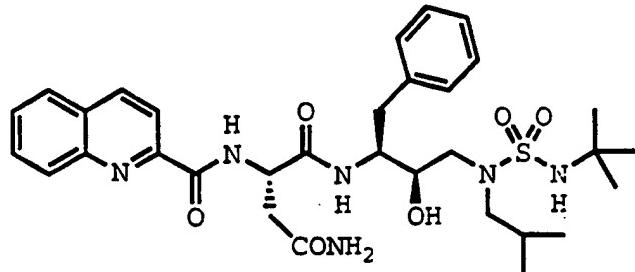
The procedures described in Example 6, Parts A-C, were used to prepare phenylmethyl [3-
15 [[(butylamino)sulfonyl](2-methylpropyl)amino]-2R-
hydroxy-1S-(phenylmethyl)propyl] carbamate. A
methanolic solution of this carbamate (460 mg, 0.796
mmoles) was hydrogenated over 10% palladium on carbon
(90 mg) to give the free amine (329 mg).

20 Part B:

The free amine from Part A (266 mg, 0.6
mmoles) was coupled with N-BOC-L-asparagine (167 mg,
0.72 mmoles) in the presence of N-hydroxybenzotriazole
25 (130mg, 0.96 mmoles) and EDC (138 mg, 0.72 mmoles) to
yield 306 mg of N1[2R-hydroxy -3-[3-
[(butylamino)sulfonyl](2-methylpropyl)amino]-1S-
(phenylmethyl)propyl]-2S-[1-(1,1-
dimethylethoxycarbonyl)amino]butane diamide after
30 purification on a silica column.

Part C:

N1[2R-hydroxy -3-[3-
[(butylamino)sulfonyl](2-methylpropyl)amino]-1S-
5 (phenylmethyl)propyl]]-2S-[(1,1-
dimethylethoxycarbonyl)amino]butane diamide (150 mg,
0.26 mmoles) was stirred in 4N HCl in dioxane (4 mL) at
r.t. for 0.5 h. Solvent and excess reagent were
evaporated to dryness. The product was dried in vacuo.
10 This material (140 mg, 0.26 mmoles) was then reacted
with 2-quinoline carboxylic acid N-hydroxysuccimide
ester (70 mg, 0.26 mmoles), DIEA (72 uL, 0.52 mmoles)
in dichloromethane (2 mL) overnight. The product -N1-
15 [3-[(butylamino)sulfonyl](2-methylpropyl)amino]-2R-
hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-
quinolinylcarbonyl)amino]butanediamide was purified by
silica gel chromatography. Anal. Calcd for
 $C_{32}H_{44}N_6O_6S$: C, 59.98; H, 6.92; N, 13.12. Found: C,
59.98; H, 6.65; N, 12.72.

Example 17

5 Preparation of N1-[3-[[(1,1-dimethyllethyl)amino]sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl-2S-[(2-quinolinylcarbonyl)amino]butanediamide

10 Part A:

A 20 mL methanol solution of phenylmethyl [2R-hydroxy -3-[[[(1,1-dimethylethyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl] carbamate from Example 8 (170 mg, 0.33 mmoles) was hydrogenated over 10% palladium on carbon (40 mg). The resulting free amine (110 mg, 0.30 mmole) was coupled with N-BOC-L-asparagine (84 mg, 0.36 mmoles) in the presence of N-hydroxybenzotriazole (65 mg, 0.48 mmoles) and EDC (69 mg, 0.36 mmoles) to yield 160 mg of N1[2R-hydroxy -3-[[[(1,1-dimethyllethyl)amino]sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2S-[(1,1-dimethylethoxycarbonyl)amino]butane diamide.

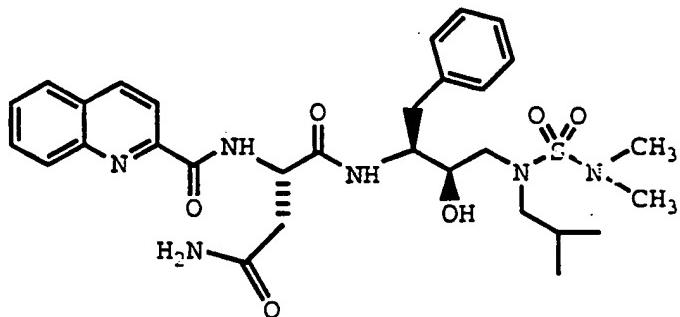
25 Part B:

N1[2R-hydroxy -3-[[[(1,1-dimethyllethyl)amino]sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2S-[(1,1-dimethylethoxycarbonyl)amino]butane diamide (150 mg, 0.25 mmole) was stirred in 4N HCl in dioxane (5 mL) at r.t.

for 0.5 h. Solvent and excess reagent were evaporated to dryness. The product was dried in vacuo. This material (135 mg, 0.25 mmoles) was then reacted with 2-quinoline carboxylic acid N-hydroxysuccimide ester (70 mg, 0.25 mmoles), DIEA (72 uL, 0.52 mmoles) in DMF (1 mL) overnight. The product N1-[3[-[(1,1-dimethyllethyl)amino]sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide was purified by 10 silica gel chromatography (85 mg, 53%). Anal. Calcd for C₃₂H₄₄N₆O₆S. 0.8 H₂O: C, 58.66; H, 7.02; N, 12.83. Found: C, 59.00; H, 6.84; N, 12.54.

Example 18

15



Preparation of N'-[3-[(N,N-dimethylamino)sulfonyl](3-
methylbutyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl-
2S-[(2-quinolinylcarbonyl)amino]butanediamide

Part A:

Preparation of N-3(S)-(Benzylloxycarbonyl)-
 amino-2(R)-hydroxy-4-phenylbutylamine, N-(3-methylbutyl).
 25 A solution of 20g (67 mmol) of N-benzylloxycarbonyl-3(S)-
 amino-1,2-(S)-epoxy-4-phenylbutane in 140 mL of isopropyl
 alcohol was treated with 83g (952 mmol) of isoamylamine
 and refluxed for one hour. The solution was cooled,
 concentrated, hexane added and the resulting solid
 30 filtered to afford 22.4g of the desired product.

Part B:

Preparation of N-3(S)-(Benzylloxycarbonyl)-
amino-2(R)-hydroxy-4-phenylbutylamine, N-(3-methylbutyl)-
5 N-(t-butyloxycarbonyl). To a solution of 22.4g (58.3
mmol) of product from Part A above, 6.48g (64.1 mmol) of
triethylamine and 150 mg of N,N-dimethyl-4-aminopyridine
in 200 mL of tetrahydrofuran at 0°C was added 12.7g (58.3
mmol) of di-t-butylpyrocarbonate in 10 mL of THF. After
10 3.5 hours at room temperature, the volatiles were
removed, ethyl acetate added and washed with 5% citric
acid, sat'd NaHCO₃, dried and concentrated to afford 30g
of crude product. Chromatography on silica gel using 20%
ethyl acetate/hexane afforded 22.5g (79%) of the desired
15 product.

Part C:

Preparation of N-3(S)-[N-benzylloxycarbonyl-L-
asparaginyl]amino-2(R)-hydroxy-4-phenylbutylamine, N-(3-
20 methylbutyl)-N-(t-butyloxycarbonyl). A solution of 22.5g
of product from Part B above in 200 mL of ethanol was
hydrogenated over 5.9g of 10% palladium-on-carbon under
50 psig hydrogen for one hour. The catalyst was filtered
and the solvent removed under reduced pressure to afford
25 15.7g of free amine. This was dissolved in 130 mL of DMF
and 4.54g (44.9 mmol) of N-methylmorpholine an added to a
mixture of 13.3g (49.9 mmol) N-benzylxy-carbonyl-L-
asparagine, 11.5g (74.9 mmol) of N-hydroxybenzotriazole
and 10.5g (54.9 mmol) of EDCI in 120 mL of DMF at 0°C,
30 which had been preactivated for one hour prior to the
addition. The mixture was stirred for 2 hours at 0°C and
then for 12 hours at room temperature. The reaction was
poured into 1L of sat'd aqueous sodium bicarbonate, the
solid collected, dissolved in ethyl acetate, washed with
35 water, sat'd sodium bicarbonate, 5% citric acid and

brine, dried and concentrated to afford 16.7g of the desired product.

Part D:

5 Preparation of N-3(S)-[N-(2-quinolinylcarbonyl)-L-asparaginyl]amino-2(R)-hydroxy-4-phenylbutylamine, N-(3-methylbutyl)-N-(t-butyloxycarbonyl). A solution of 16.7g (28.0 mmol) of product from Part C in 250 mL of methanol was
10 hydrogenated over 6.0g of 10% palladium-on-carbon and under 50 psig hydrogen for one hour. The catalyst was filtered and the solution concentrated to afford 10.0g of free amine. This was dissolved in 100 mL of methylene chloride, 4.35g (43 mmol) of N-methylmorpholine was
15 added followed by 5.53g (20.5 mmol) of quinoline-2-carboxylic acid, N-hydroxysuccinimide ester. This was stirred at room temperature overnight, the solvent removed, ethyl acetate added and washed with 5% citric acid, sat'd sodium bicarbonate, brine, dried and
20 concentrated to afford 14g of crude product.

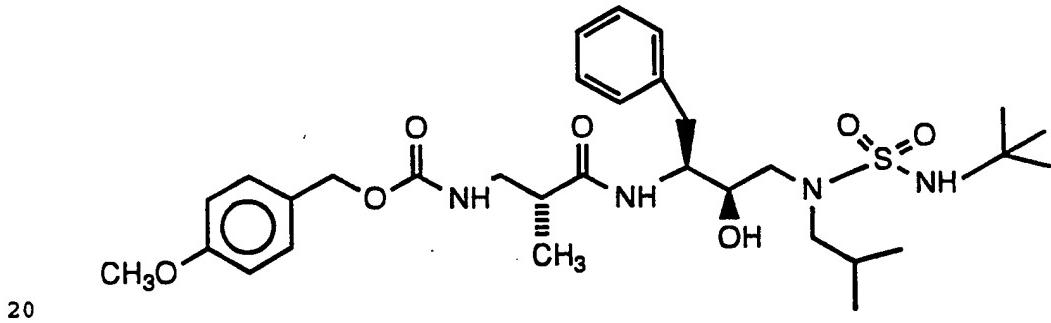
Recrystallization from ethyl acetate and hexane afforded 10.5g (83%) of desired product.

Part E:

25 Preparation of N-3(S)-[N-(2-quinolinylcarbonyl)-L-asparaginyl]amino-2(R)-hydroxy-4-phenylbutylamine, N-(3-methylbutyl). To 80 mL of 4N hydrochloric acid in dioxane was added 9.17g (14.8 mmol) of product from Part D above. After one hour, the
30 product becomes gummy. The solvents were removed, diethyl ether added and removed and the residue dissolved in 20 mL of methanol. This solution was added to 400 mL of sat'd aqueous sodium bicarbonate, the solids collected, washed with acetone and hexane and dried in
35 vacuo over P₂O₅ to afford 4.75g of the desired product.

Part E:

To a solution of 200 mg (0.38 mmol) of the amino alcohol from Part E above in 10 mL of anhydrous tetrahydrofuran and 0.3 mL of N,N-dimethylformamide, was 5 added 42 mg (0.42 mmol) of triethylamine and then 55 mg (0.38 mmol) of dimethylsulfamoyl chloride. After stirring from twenty hours at room temperature, the volatiles were removed in vacuo, ethyl acetate added and the solution washed with 5% aqueous citric acid, 10 saturated aqueous sodium bicarbonate and saturated brine. The organic layer was dried and concentrated to afford 166 mg of crude product, which was chromatographed on silica gel using a gradient of 1-10% isopropanol in methylene chloride to afford 119 mg of pure product, 15 m/e 627 (M+H). Calcd. for $C_{31}H_{42}N_6O_6S$ 627.2965, found 627.2998.

Example 19

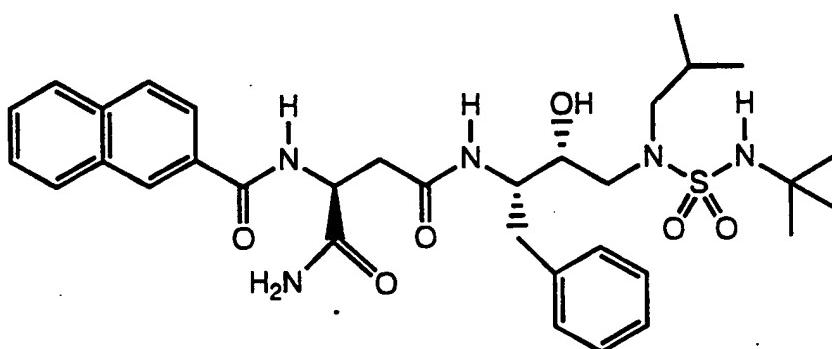
Preparation of [[(4-methoxyphenyl)methyl][3-[3-[[3-((1,1-dimethylethyl)aminosulfonyl)(2-methylpropyl)aminol-2R-hydroxy-1S-(phenylmethyl)propyl]aminol-2R-methyl-3-
25 oxopropyl]carbamate

To a solution of 83 mg (0.31 mmol) of N-(4-methoxy)benzyloxycarbonyl 2R-methyl-3-aminopropionic acid and 71 mg (0.46 mmol) of N-hydroxybenzotriazole in 2 mL 30 of anhydrous N,N-dimethylformamide (DMF) at 0°C, was

added 65 mg (0.34 mmol) of 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride. After two hours at 0°C, a solution of 104 mg (0.28 mmol) of free amine from example 8, part C in 0.5 mL of DMF was added. After two hours at 0°C and fourteen hours at room temperature, the DMF was removed in vacuo, ethyl acetate added, washed with saturated aqueous sodium bicarbonate, brine, dried over anhydrous magnesium sulfate, filtered and concentrated to afford 200 mg of crude material. This was chromatographed on silica gel using 3% methanol/methylene chloride to afford 120 mg of product, which was further purified by crystallization from diethyl ether/hexane to afford 25 mg (13%) of the desired product m/e = 627 (M+Li).

15

Example 20



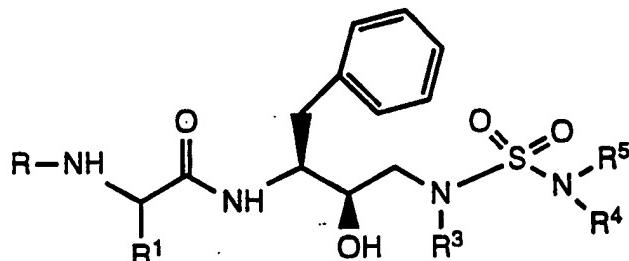
20 Preparation of N4-[3-[[[(1,1-dimethyllethyl)aminol-sulfonyl](2-methylpropyl)aminol-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)-aminolbutanediamide

25 107 mg (0.37 mmol) of N-2-(quinoylcarbonyl)-L-
isoasparagine and 76 mg (1.5 eq) of N-hydroxysuccinamide
were dissolved in 2 mL of dimethylformamide and cooled to
zero degrees C. To this was added 111 mg (0.37 mmol) of
EDC and the solution stirred for 20 minutes. To this
30 cooled solution was added 140 mg (0.37 mmol) of the free

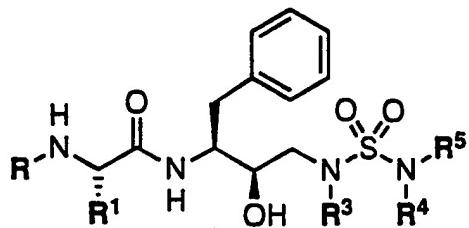
amine from example 8, part C and the reaction was returned to room temperature and stirred for 18 hours. The dimethylformamide was removed by evaporation and the residue was partitioned between ethyl acetate and 5 saturated sodium bicarbonate. The organic layer was washed with 5% KHSO_4 and brine, dried over magnesium sulfate, filtered and concentrated to yield 216 mg of crude solid, which was chromatographed using ethyl acetate:methanol:hexane, 95:5:50 to yield 110 mg (4.8% 10 yield) of pure product, m/e = 641 ($\text{M}+\text{H}$).

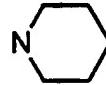
Example 21

Following the procedures of Examples 1-20, the 15 compounds shown in Tables 3A and 3B were prepared.

TABLE 3A

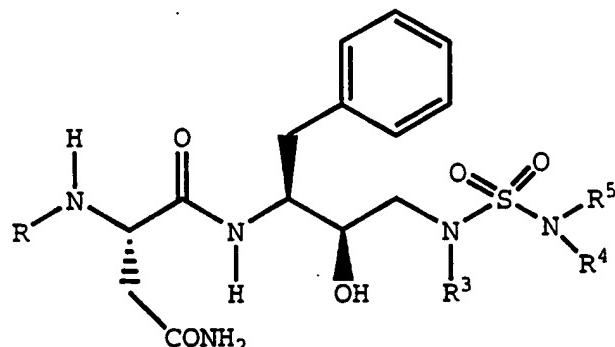
Entry No.	R	R ¹	R ³	R ⁴	R ⁵	
1	Cbz	t-Butyl	i-Amyl	Methyl	Methyl	
10	Q	t-Butyl	i-Amyl	Methyl	Methyl	
3	Cbz	i-Butyl	i-Butyl	Methyl	Hydrogen	
4	N,N-Dimethylglycine	t-Butyl	i-Butyl	n-Butyl	Hydrogen	
5	N,N-Dimethylglycine	t-Butyl	i-Butyl	Methyl	Hydrogen	
6	Q	CH ₂ C(O)NH ₂	i-Butyl	n-Butyl	Hydrogen	
15	7	Q	CH ₂ C(O)NH ₂	i-Butyl	t-Butyl	Hydrogen
	8	Q	CH ₂ C(O)NH ₂	i-Butyl		
9	Q	CH ₂ C(O)NH ₂	i-Butyl	Phenyl	Hydrogen	
10	Q	CH ₂ C(O)NH ₂	i-Butyl	Cyclohexyl	Hydrogen	

TABLE 3B

	Entry	R	R ¹	R ³	R ⁴	R ⁵
10	A	Cbz	t-butyl	isoamyl	methyl	methyl
	B	Cbz	t-butyl	isobutyl	methyl	H
	C	N,N-Dimethylglycine	t-butyl	isobutyl	methyl	H
15	D	Q	CH ₂ CONH ₂	isobutyl	cyclohexyl	H
	E	Q	CH ₂ CONH ₂	isobutyl	phenyl	H
F N,N-Dimethylglycine t-butyl isobutyl				NR ⁴ R ⁵ =		

Utilizing the procedures set forth above, the compounds shown in Tables 4-14 could be prepared. Thus, utilizing the intermediates of Examples 1-10 according to the procedures in Examples 14-21, the compounds shown in Tables 4-16 could be prepared.

TABLE 4



Entry No.	R	R ³	R ⁴	R ⁵
1	Cbz ^a	CH ₃	n-Butyl	CH ₃
2	Cbz	i-Butyl	CH ₃	C ₆ H ₅
3	Cbz	i-Butyl	n-Butyl	H
4	Q ^b	i-Butyl	n-Butyl	H
5	Cbz	i-Propyl	n-Butyl	H
6	Q	i-Propyl	n-Butyl	CH ₃
7	Cbz	C ₆ H ₅	n-Butyl	H
8	Cbz	-CH ₂ -	n-Butyl	H
9	Cbz	-CH ₂ -	n-Butyl	H
10	Q	-CH ₂ -	n-Butyl	H
11	Cbz		n-Butyl	H
12	Cbz	i-Butyl	n-Propyl	H

TABLE 4 (Cont'd.)

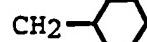
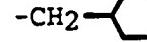
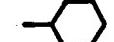
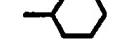
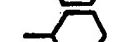
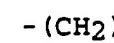
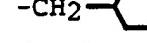
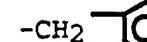
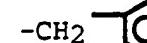
Entry No.	R	R ³	R ⁴	R ⁵
13	Cbz	i-Butyl	-CH ₂ CH(CH ₃) ₂	H
14	Cbz	(R)-CH(CH ₃)- 	n-Butyl	H
15	Cbz	CH ₂ - 	i-Propyl	H
16	Cbz	-CH ₂ - 	-CH ₂ CH ₂ CH(CH ₃) ₂	H
17	Cbz	i-Butyl	-CH ₂ CH ₃	H
18	Cbz	i-Butyl	-CH(CH ₃) ₂	H
19	Cbz	i-Butyl	 	H
20	Q	n-Butyl	 	H
21	Cbz	-CH ₂ - 	-(CH ₂) ₂ CH(CH ₃) ₂	H
22	Cbz	(CH ₂) ₂ CH(CH ₃) ₂	-CH(CH ₃) ₂	H
23	Q	i-Butyl	-CH(CH ₃) ₂	H
24	Cbz	i-Butyl	-C(CH ₃) ₃	H
25	Q	i-Butyl	-C(CH ₃) ₃	H
26	Cbz	-CH ₂ - 	-C(CH ₃) ₃	H
27	Q	-CH ₂ - 	-C(CH ₃) ₃	H
28	Cbz	-(CH ₂) ₂ CH(CH ₃) ₂	-C(CH ₃) ₃	CH ₃
29	Q	-(CH ₂) ₂ CH(CH ₃) ₂	-C(CH ₃) ₃	CH ₃
30	Cbz	-CH ₂ C ₆ H ₅	-C(CH ₃) ₃	H
31	Q	-CH ₂ C ₆ H ₅	-C(CH ₃) ₃	H
32	Cbz	-(CH ₂) ₂ C ₆ H ₅	-C(CH ₃) ₃	CH ₃
33	Cbz	-(CH ₂) ₂ C ₆ H ₅	-C(CH ₃) ₃	H
34	Cbz	n-Butyl	-C(CH ₃) ₃	H

TABLE 4 (Cont'd.)

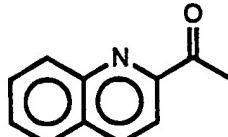
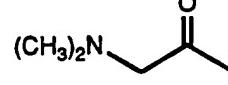
Entry No.	R	R ³	R ⁴	R ⁵
35	Cbz	n-Pentyl	-C(CH ₃) ₃	H
36	Cbz	n-Hexyl	-C(CH ₃) ₃	H
37	Cbz	-CH ₂ - 	-C(CH ₃) ₃	H
38	Cbz	-CH ₂ C(CH ₃) ₃	-C(CH ₃) ₃	H
39	Q	-CH ₂ C(CH ₃) ₃	-C(CH ₃) ₃	H
40	Cbz	-CH ₂ CH ₂ -N 	-C(CH ₃) ₃	H
41	Cbz	-CH ₂ C ₆ H ₅ OCH ₃ (para)	-C(CH ₃) ₃	H
42	Cbz	-CH ₂ - 	-C(CH ₃) ₃	H
43	Cbz	-CH ₂ - 	-C(CH ₃) ₃	H
44	Cbz	-(CH ₂) ₂ C(CH ₃) ₃	-C(CH ₃) ₃	H
45	Q	-(CH ₂) ₂ C(CH ₃) ₃	-C(CH ₃) ₃	H
46	Cbz	-(CH ₂) ₄ OH	-C(CH ₃) ₃	H
47	Q	-(CH ₂) ₄ OH	-C(CH ₃) ₃	H
48	Q	-CH ₂ - 	-C(CH ₃) ₃	H
49	Q	-CH ₂ - 	-C(CH ₃) ₃	H
50	Cbz	-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	H
51		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	Me
52	(CH ₃) ₂ N 	-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	H

TABLE 4 (Cont'd.)

Entry No.	R	R ³	R ⁴	R ⁵
53		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	H
54		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	H
55		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	Me
56		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	H
57		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	Me
58		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	Me
59		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	H

TABLE 4 (Cont'd.)

<u>Entry</u> <u>No.</u>	<u>R</u>	<u>R</u> ³	<u>R</u> ⁴	<u>R</u> ⁵
60		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	Me
61		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	H
62		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	H
63		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	H
64		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	Me
65		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	H

TABLE 4 (Cont'd.)

Entry No.	R	R ³	R ⁴	R ⁵
66		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	H
67		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	H
68		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	H
69		-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅	H
70	Q	-CH ₂ Ph	-Ph	H
71	Q	-CH ₂ --F	-Ph	H
72	Q	-CH ₂ -	-Ph	H
73	Q	-CH ₂ --OCH ₃	-Ph	H
74	Q	-CH ₂ -	-Ph	H

TABLE 4 (Cont'd.)

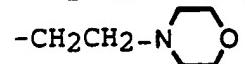
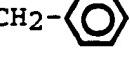
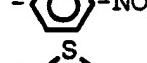
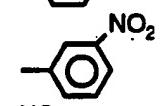
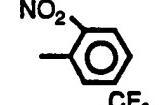
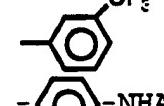
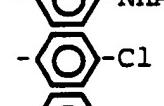
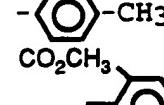
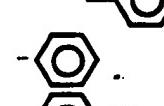
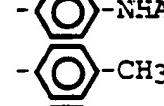
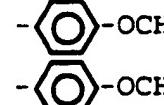
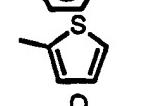
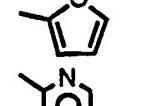
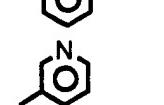
<u>Entry</u>	<u>R</u>	<u>R³</u>	<u>R⁴</u>	<u>R⁵</u>
<u>No.</u>				
75	Q	-CH ₂ - 	-Ph	H
76	Q	-CH ₂ CH=CH ₂	-Ph	H
77	Q	- 	-Ph	H
78	Q	- 	-Ph	H
79	Q	-CH ₂ CH ₂ Ph	-Ph	H
80	Q	-CH ₂ CH ₂ CH ₂ CH ₂ OH	-Ph	H
81	Q	-CH ₂ CH ₂ N(CH ₃) ₂	-Ph	H
82	Q	-CH ₂ CH ₂ - 	-Ph	H
83	Q	-CH ₃	-Ph	H
84	Q	-CH ₂ CH ₂ CH ₂ SCH ₃	-Ph	H
85	Q	-CH ₂ CH ₂ CH ₂ S(O) ₂ CH ₃	-Ph	H
86	Q	-CH ₂ CH ₂ CH ₂ CH(CH ₃) ₂	- 	H
87	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₂ - 	H
88	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₂ CH ₂ CH ₃	H
89	Q	-CH ₂ CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₃	H
90	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	- 	H
91	Q	-CH ₂ CH ₂ CH(CH ₃) ₂		H
92	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	- 	H
93	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	- 	H

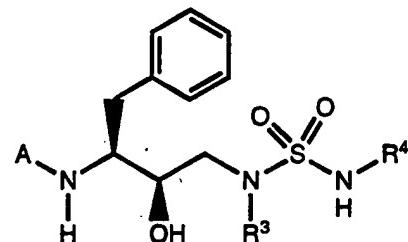
TABLE 4 (Cont'd.)

<u>Entry No.</u>	<u>R</u>	<u>R³</u>	<u>R⁴</u>	<u>R⁵</u>
94	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	- 	H
95	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	- 	H
96	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	- 	H
97	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	- 	H
98	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	- 	H
99	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	- 	H
100	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	- 	H
101	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	- 	
102	Q	-CH ₂ CH ₂ CH(CH ₃) ₂	- 	H
103	Q	-CH ₂ CH(CH ₃) ₂	- 	H
104	Q	-CH ₂ CH(CH ₃) ₂	- 	H
105	Q	-CH ₂ CH(CH ₃) ₂	- 	H
106	Q	-CH ₂ CH ₂ CH ₃	- 	H
107	Q	-CH ₂ CH ₂ CH ₂ CH ₃	- 	H
108	Q	-CH ₂ CH ₂ CH ₃	- 	H
109	Q	-CH ₂ CH ₂ CH ₃	- 	H
110	Q	-CH ₂ CH ₂ CH ₃		
111	Q	-CH ₂ CH ₂ CH ₃		H

a benzyloxycarbonyl

b 2-quinolinylcarbonyl

TABLE 5



Entry No.	A	R ³	R ⁴
1	Cbz-Val	i-amyl	-C ₆ H ₅
2	Cbz-Leu	i-amyl	-C ₆ H ₅
3	Cbz-Ile	i-amyl	-C ₆ H ₅
4	Ac-D-homo-Phe	i-Bu	methyl
5	Qui-Orn(g-Cbz)	-CH ₂ -	-C ₆ H ₅
6	Cbz-Asn	-CH ₂ CH=CH ₂	-C ₆ H ₅
7	Acetyl-t-BuGly	i-amyl	-C ₆ H ₅
8	Acetyl-Phe	i-amyl	-C ₆ H ₅
9	Acetyl-Ile	i-amyl	-C ₆ H ₅
10	Acetyl-Leu	i-amyl	-C ₆ H ₅
11	Acetyl-His	i-amyl	-C ₆ H ₅
12	Acetyl-Thr	i-amyl	-C ₆ H ₅
13	Acetyl-NHCH(C(CH ₃) ₂ (SCH ₃))C(O)-	i-amyl	-C ₆ H ₅
14	Cbz-Asn	i-amyl	-C ₆ H ₅
15	Cbz-Ala	i-amyl	-C ₆ H ₅
16	(N,N-dimethylglycinyl)Val	i-amyl	-C ₆ H ₅
17	(N-methylglycinyl)Val	i-amyl	-C ₆ H ₅
18	(N,N-dimethylglycinyl)Ile	i-amyl	-C ₆ H ₅
19	(N-methylglycinyl)Ile	i-amyl	-C ₆ H ₅

TABLE 5 (Cont'd)

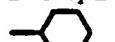
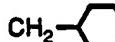
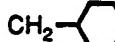
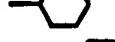
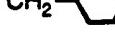
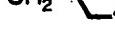
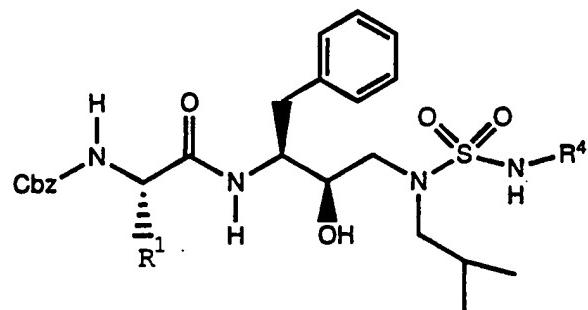
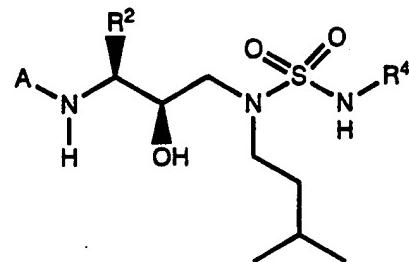
Entry	A	R ³	R ⁴
20	(N,N-dimethylglycinyl)Val	i-butyl	n-butyl
21	(N,N-dimethylglycinyl)Val	i-amyl	n-butyl
22	(N,N-dimethylglycinyl)Val		n-butyl
23	(N,N-dimethylglycinyl)Val		n-butyl
24	(N,N-dimethylglycinyl)Ile	i-butyl	n-butyl
25	(N,N-dimethylglycinyl)Ile	i-amyl	n-butyl
26	(N,N-dimethylglycinyl)Ile		n-butyl
27	(N,N-dimethylglycinyl)Ile		n-butyl
20	Cbz-Ala	i-amyl	-C ₆ H ₅
21	Cbz-beta-cyanoAla	i-amyl	-C ₆ H ₅
22	Cbz-t-BuGly	i-amyl	-C ₆ H ₅
23	Q-t-BuGly	i-amyl	-C ₆ H ₅
24	Q-SCH ₃ Cys	i-amyl	-C ₆ H ₅
25	Cbz-SCH ₃ Cys	i-amyl	-C ₆ H ₅
26	Q-Asp	i-amyl	-C ₆ H ₅
27	Cbz-(NHCH(C(CH ₃) ₂ (SCH ₃))C(O)-	i-amyl	-C ₆ H ₅
28	Cbz-EtGly	i-amyl	-C ₆ H ₅
29	Cbz-PrGly	i-amyl	-C ₆ H ₅
30	Cbz-Thr	i-amyl	-C ₆ H ₅
31	Q-Phe	i-amyl	-C ₆ H ₅
32	Cbz-Phe	i-amyl	-C ₆ H ₅
33	(N,N-dimethylglycinyl)Val	i-butyl	t-butyl
34	(N,N-dimethylglycinyl)Val	i-amyl	t-butyl
35	(N,N-dimethylglycinyl)Val		t-butyl
36	(N,N-dimethylglycinyl)Val		t-butyl
37	(N,N-dimethylglycinyl)Ile	i-butyl	t-butyl
38	(N,N-dimethylglycinyl)Ile	i-amyl	t-butyl
39	(N,N-dimethylglycinyl)Ile		t-butyl
40	(N,N-dimethylglycinyl)Ile		t-butyl

TABLE 6

Entry	R ¹	R ⁴
1	CH ₂ SO ₂ CH ₃	t-butyl
2	(R)-CH(OH)CH ₃	t-butyl
3	CH(CH ₃) ₂	t-butyl
4	(R,S)CH ₂ SOCH ₃	t-butyl
5	CH ₂ SO ₂ NH ₂	t-butyl
6	CH ₂ SCH ₃	t-butyl
7	CH ₂ CH(CH ₃) ₂	t-butyl
8	CH ₂ CH ₂ C(O)NH ₂	t-butyl
9	(S)-CH(OH)CH ₃	t-butyl
10	-CH ₂ C≡C-H	t-butyl

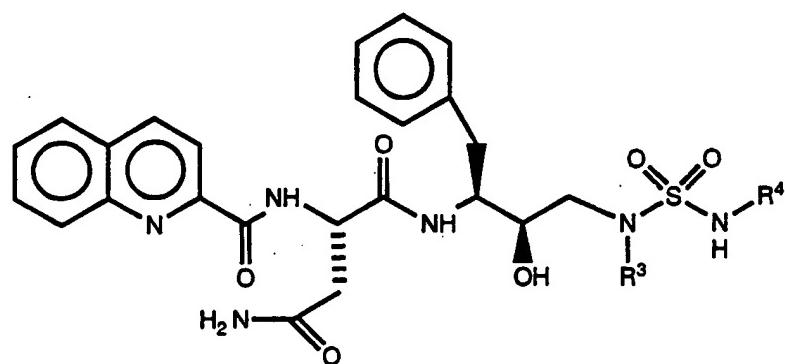
TABLE 7

Entry	R ²	A	R ⁴
1	n-Bu	Cbz-Asn	t-butyl
2	cyclohexylmethyl	Cbz-Asn	t-butyl
3	n-Bu	Boc	t-butyl
4	n-Bu	Cbz	t-butyl
5	C ₆ H ₅ CH ₂	Boc	t-butyl
6	P-F-C ₆ H ₅ CH ₂	Cbz	t-butyl
7	C ₆ H ₅ CH ₂	benzoyl	t-butyl
8	cyclohexylmethyl	Cbz	t-butyl
9	n-Bu	Q-Asn	t-butyl
10	cyclohexylmethyl	Q-Asn	t-butyl
11	C ₆ H ₅ CH ₂	Cbz-Ile	t-butyl
12	C ₆ H ₅ CH ₂	Q-Ile	t-butyl
13	P-F-C ₆ H ₅ CH ₂	Cbz-t-BuGly	t-butyl
14	C ₆ H ₅ CH ₂	Q-t-BuGly	t-butyl
15	C ₆ H ₅ CH ₂	Cbz-Val	t-butyl
16	C ₆ H ₅ CH ₂	Q-Val	t-butyl
17	2-naphthylmethyl	Cbz-Asn	t-butyl
18	2-naphthylmethyl	Q-Asn	t-butyl
19	2-naphthylmethyl	Cbz	t-butyl
20	n-Bu	Cbz-Val	t-butyl
21	n-Bu	Q-Val	t-butyl
22	n-Bu	Q-Ile	t-butyl
23	n-Bu	Cbz-t-BuGly	t-butyl

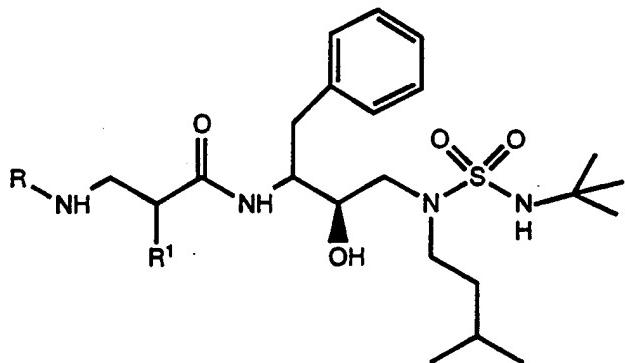
Entry	R ²	A	R ⁴
1	n-Bu	Cbz-Asn	t-butyl
2	cyclohexylmethyl	Cbz-Asn	t-butyl
3	n-Bu	Boc	t-butyl
4	n-Bu	Cbz	t-butyl
5	C ₆ H ₅ CH ₂	Boc	t-butyl
6	P-F-C ₆ H ₅ CH ₂	Cbz	t-butyl
7	C ₆ H ₅ CH ₂	benzoyl	t-butyl
8	cyclohexylmethyl	Cbz	t-butyl
9	n-Bu	Q-Asn	t-butyl
10	cyclohexylmethyl	Q-Asn	t-butyl
11	C ₆ H ₅ CH ₂	Cbz-Ile	t-butyl
12	C ₆ H ₅ CH ₂	Q-Ile	t-butyl
13	P-F-C ₆ H ₅ CH ₂	Cbz-t-BuGly	t-butyl
14	C ₆ H ₅ CH ₂	Q-t-BuGly	t-butyl
15	C ₆ H ₅ CH ₂	Cbz-Val	t-butyl
16	C ₆ H ₅ CH ₂	Q-Val	t-butyl
17	2-naphthylmethyl	Cbz-Asn	t-butyl
18	2-naphthylmethyl	Q-Asn	t-butyl
19	2-naphthylmethyl	Cbz	t-butyl
20	n-Bu	Cbz-Val	t-butyl
21	n-Bu	Q-Val	t-butyl
22	n-Bu	Q-Ile	t-butyl
23	n-Bu	Cbz-t-BuGly	t-butyl

TABLE 7 (Cont'd.)

Entry	R ²	A	R ⁴
24	n-Bu	Q-t-BuGly	t-butyl
25	p-F(C ₆ H ₄)CH ₂	Q-Asn	t-butyl
26	p-F(C ₆ H ₄)CH ₂	Cbz	t-butyl
27	p-F(C ₆ H ₄)CH ₂	Cbz-Asn	t-butyl
28	C ₆ H ₅ CH ₂	Cbz-propargylglycine	t-butyl
29	C ₆ H ₅ CH ₂	Q-propargylglycine	t-butyl
30	C ₆ H ₅ CH ₂	acetylpropargylglycine	t-butyl

TABLE 8

Entry	R^3	R^4
1	$-CH_2CH(CH_3)_2$	$-C(CH_3)_2$
2	$-CH_2CH_2CH(CH_3)_2$	
3	$-CH_2CH_2CH(CH_3)_2$	
4	$-CH_2CH_2CH(CH_3)_2$	
5	$-CH_2CH_2CH(CH_3)_2$	

TABLE 9

Entry	R	R ¹
1		-CH ₃
2		-CH ₃
3		-CH(CH ₃) ₂
4		-CH(CH ₃) ₂
5		-C(CH ₃) ₃
6		-CH ₃
7		-CH ₃

Table 9 (Cont'd)

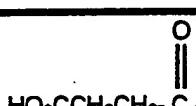
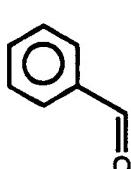
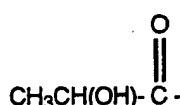
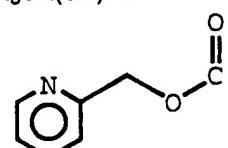
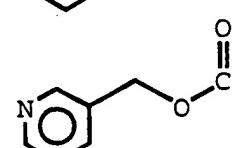
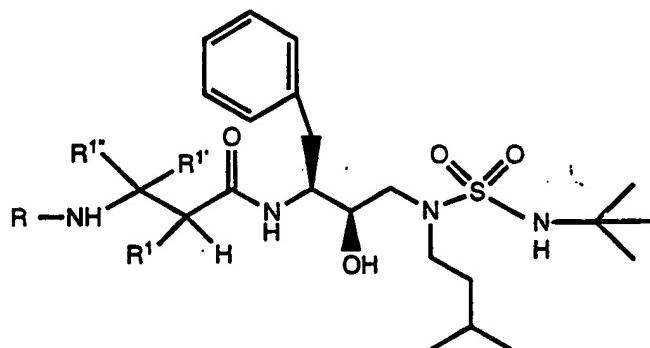
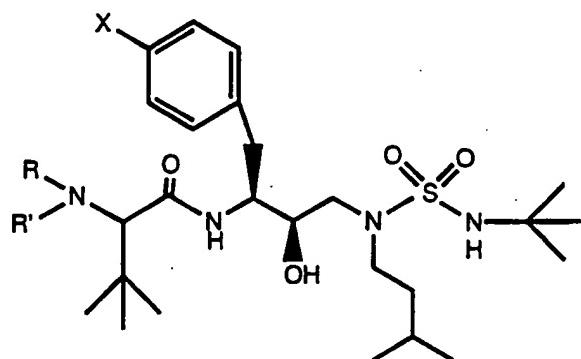
Entry	R	R ¹
8		-CH ₃
9		-CH ₃
10		-CH ₃
11		-CH ₃
12		-CH ₃
13		-CH ₃
14		-CH ₃
15		-CH ₃
16		-CH ₃

TABLE 9 (Cont'd)

Entry	R	R^1
17		$-CH_3$
18		
19		

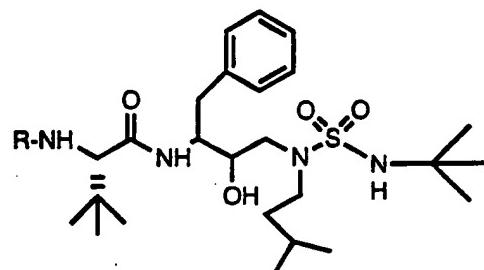
TABLE 10

Entry	R ¹	R ^{1'}	R ^{1''}	R
1	H	H	H	
2	H	H	H	
3	H	CH ₃	H	
4	H	CH ₃	CH ₃	
5	H	H	CO ₂ CH ₃	
6	H	H	H	
7	H	H	H	
8	H	H	CONH ₂	Cbz
9	H	H	CONH ₂	2-quinolinyloxycarbonyl

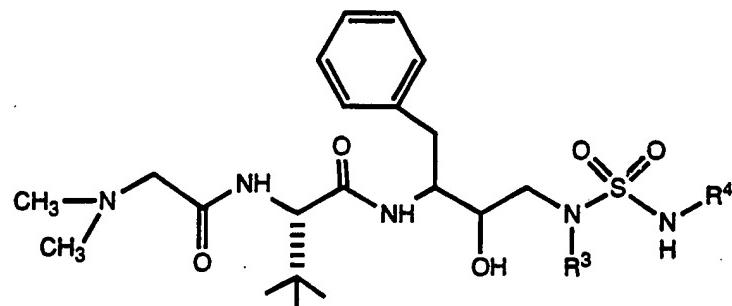
TABLE 11

Entry	R	R'	X
1	R=H	R'=H	X=H
2	R=Me	R'=Me	X=H
3	R=H	R'=Me	X=H
4	R=Me	R'=Me	X=F
5	R=H	R'=Me	X=F
6	R=Cbz	R'=Me	X=H
7	R=H	R'=Bz	X=H
8	R+R'=pyrrole	X=H	

TABLE 12



Entry	Acyl Group (R)
1	benzyloxycarbonyl
2	<u>tert</u> -butoxycarbonyl
3	acetyl
4	2-quinoylcarbonyl
5	phenoxyacetyl
6	benzoyl
7	methyloxaloyl
8	pivaloyl
9	trifluoracetyl
10	bromoacetyl
11	hydroxyacetyl
12	morpholinylacetyl
13	N,N-dimethylaminoacetyl
14	N-benzylaminoacetyl
15	N-phenylaminoacetyl
16	N-benzyl-N-methylaminoacetyl
17	N-methyl-N-(2-hydroxyethyl)aminoacetyl
18	N-methylcarbamoyl
19	3-methylbutyryl
20	N-isobutylcarbamoyl
21	succinoyl (3-carboxypropionyl)
22	carbamoyl
23	N-(2-indanyl)aminoacetyl
24	N-methylaminoacetyl

TABLE 13

Entry	R ³	R ⁴
1	-CH ₃	-n-Butyl
2	-n-Butyl	-CH ₃
3	-i-Butyl	-n-Butyl
4	-i-Propyl	-n-Butyl
5	-C ₆ H ₅	-n-Butyl
6	-CH ₂ -	-n-Butyl
7	-CH ₂ -	-n-Butyl
8		-n-Butyl
9	-i-Butyl	-n-Propyl
10	-i-Butyl	-CH ₂ CH(CH ₃) ₂
11	-(R)-CH(CH ₃)-	-n-Butyl
12	-CH ₂ -	-i-Propyl
13	-CH ₂ -	-CH ₂ CH ₂ CH(CH ₃) ₂
14	i-Butyl	-CH ₂ CH ₃
15	i-Butyl	-CH(CH ₃) ₂
16	i-Butyl	

TABLE 13 (Cont'd)

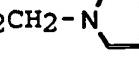
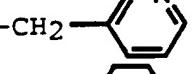
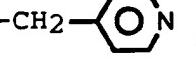
Entry	R ³	R ⁴
17	-CH ₂ - 	- (CH ₂) ₂ CH(CH ₃) ₂
18	(CH ₂) ₂ CH(CH ₃) ₂	-CH(CH ₃) ₂
19	i-Butyl	-CH(CH ₃) ₂
20	i-Butyl	-C(CH ₃) ₃
21	-CH ₂ - 	-C(CH ₃) ₃
22	- (CH ₂) ₂ CH(CH ₃) ₂	-C(CH ₃) ₃
23	-CH ₂ C ₆ H ₅	-C(CH ₃) ₃
24	- (CH ₂) ₂ C ₆ H ₅	-C(CH ₃) ₃
25	n-Butyl	-C(CH ₃) ₃
26	n-Pentyl	-C(CH ₃) ₃
27	n-Hexyl	-C(CH ₃) ₃
28	-CH ₂ - 	-C(CH ₃) ₃
29	-CH ₂ C(CH ₃) ₃	-C(CH ₃) ₃
30	-CH ₂ CH ₂ -N 	-C(CH ₃) ₃
31	-CH ₂ C ₆ H ₅ OCH ₃ (para)	-C(CH ₃) ₃
32	-CH ₂ - 	-C(CH ₃) ₃
33	-CH ₂ - 	-C(CH ₃) ₃
34	- (CH ₂) ₂ C(CH ₃) ₃	-C(CH ₃) ₃
35	- (CH ₂) ₄ OH	-C(CH ₃) ₃
36	-CH ₂ -  -F	-C(CH ₃) ₃

TABLE 13 (Cont'd)

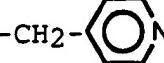
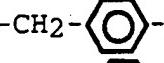
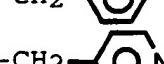
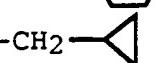
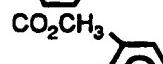
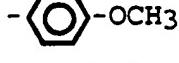
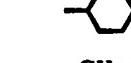
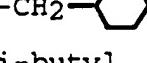
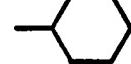
Entry	R ³	R ⁴
37	-CH ₂ - 	-C(CH ₃) ₃
38	-CH ₂ CH(CH ₃) ₂	-C ₆ H ₅
39	i-amyl	-CH ₂ C(CH ₃) ₃
40		-CH ₂ C(CH ₃) ₃
41	CH ₃ 	-CH ₂ C(CH ₃) ₃
42	i-butyl	-CH ₂ C(CH ₃) ₃
43	-CH ₂ Ph	-Ph
44	-CH ₂ - 	-Ph
45	-CH ₂ - 	-Ph
46	-CH ₂ - 	-Ph
47	-CH ₂ - 	-Ph
48	-CH ₂ 	-Ph
49	-CH ₂ CH=CH ₂	-Ph
50		-Ph
51		-Ph
52	-CH ₂ CH ₂ Ph	-Ph
53	-CH ₂ CH ₂ CH ₂ CH ₂ OH	-Ph
54	-CH ₂ CH ₂ N(CH ₃) ₂	-Ph
55	-CH ₂ CH ₂ -N 	-Ph
56	-CH ₃	-Ph

TABLE 13 (Cont'd)

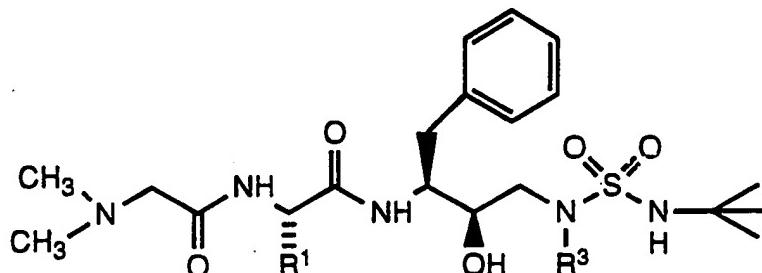
Entry	R ³	R ⁴
57	-CH ₂ CH ₂ CH ₂ SCH ₃	-Ph
58	-CH ₂ CH ₂ CH ₂ S(O) ₂ CH ₃	-Ph
59	-CH ₂ CH ₂ CH(CH ₃) ₂	- 
60	-CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₂ - 
61	-CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₂ CH ₂ CH ₃
62	-CH ₂ CH ₂ CH(CH ₃) ₂	-CH ₃
63	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -F
64	-CH ₂ CH ₂ CH(CH ₃) ₂	- 
65	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -NO ₂
66	-CH ₂ CH ₂ CH(CH ₃) ₂	- 
67	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -OCH ₃
68	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -NO ₂
69	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -CF ₃
70	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -NHAc
72	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -Cl

TABLE 13 (Cont'd)

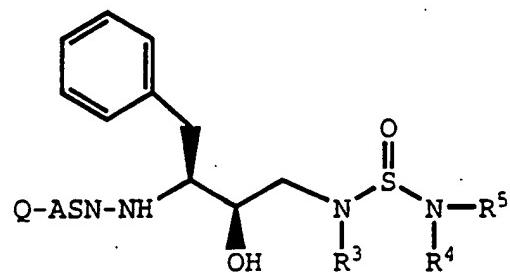
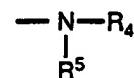
entry	R ³	R ⁴
73	-CH ₂ CH ₂ CH(CH ₃) ₂	-  -CH ₃
74	-CH ₂ CH ₂ CH(CH ₃) ₂	- 
75	-CH ₂ CH(CH ₃) ₂	- 
76	-CH ₂ CH(CH ₃) ₂	- 
77	-CH ₂ CH(CH ₃) ₂	- 
78	-CH ₂ CH(CH ₃) ₂	- 
79	-CH ₂ CH ₂ CH ₃	- 
80	-CH ₂ CH ₂ CH ₂ CH ₃	- 
81	i-butyl	t-butyl
82	i-amyl	t-butyl
83	- 	t-butyl
84	-CH ₂ - 	t-butyl
85	i-butyl	- 

a benzyloxycarbonyl

b 2-quinolinylcarbonyl

Table 14

Entry	R ¹	R ³
1	C(CH ₃) ₃	CH ₂ CH ₂ CH(CH ₃) ₂
2	CH ₂ C≡CH	CH ₂ CH ₂ CH(CH ₃) ₂
3	C(CH ₃) ₂ (SCH ₃)	CH ₂ CH ₂ CH(CH ₃) ₂
4	C(CH ₃) ₂ (S[O]CH ₃)	CH ₂ CH ₂ CH(CH ₃) ₂
5	C(CH ₃) ₂ (S[O] ₂ CH ₃)	CH ₂ CH ₂ CH(CH ₃) ₂
6	C(CH ₃) ₃	CH ₂ CH(CH ₃) ₂
7	C(CH ₃) ₃	-C ₆ H ₅
8	CH(CH ₃) ₂	CH ₂ CH(CH ₃) ₂
9	CH(CH ₂ CH ₃)(CH ₃)	CH ₂ CH(CH ₃) ₂

TABLE 15 R_3 

$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	$-\text{N}(\text{CH}_3)_2$
$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	$-\text{N}(\text{CH}_2\text{CH}_3)_2$
$-\text{CH}_2\text{CH}(\text{CH}_3)_2$	$-\text{N}(\text{CH}(\text{CH}_3)_2)_2$

$-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$	$-\text{N}(\text{CH}_3)_2$
$-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$	$-\text{N}(\text{CH}_2\text{CH}_3)_2$
$-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$	

	$-\text{N}(\text{CH}_3)_2$
	$-\text{N}(\text{CH}_2\text{CH}_3)_2$

$-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$	
---------------------------------------------------	--

$-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$	
---------------------------------------------------	--

TABLE 15 (Cont'd.)

R_3	$\begin{array}{c} \text{---} \\ \\ \text{N---R}_4 \\ \\ \text{R}_5 \end{array}$
$-\text{CH}_2-\text{C}_6\text{H}_3\text{F}_2$	$\begin{array}{c} \text{---} \\ \\ \text{N} \\ \\ \text{C}_6\text{H}_11 \end{array}$
$-\text{CH}_2-\text{C}_6\text{H}_3\text{F}_2$	$\begin{array}{c} \text{---} \\ \\ \text{N} \\ \\ \text{C}_6\text{H}_11 \end{array}$
$-\text{CH}_2-\text{C}_6\text{H}_3\text{F}_2$	$\text{N}(\text{CH}_3)(t\text{-Bu})$
$-\text{CH}_2-\text{C}_6\text{H}_3\text{F}_2$	$\begin{array}{c} \text{CH}_3 \\ \\ \text{---} \\ \\ \text{N} \\ \\ \text{C}_6\text{H}_11 \end{array}$
$-\text{CH}_2-\text{C}_6\text{H}_3\text{F}_2$	$\begin{array}{c} \text{---} \\ \\ \text{N} \\ \\ \text{C}_6\text{H}_11 \end{array}$
$-\text{CH}_2-\text{C}_6\text{H}_3\text{F}_2$	$\begin{array}{c} \text{---} \\ \\ \text{N} \\ \\ \text{C}_6\text{H}_11 \end{array}$

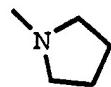
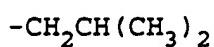
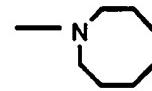
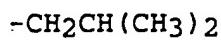
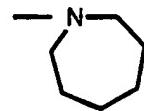
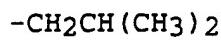
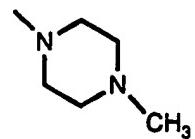
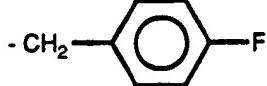
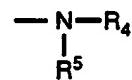
TABLE 15 (Cont'd.)R₃

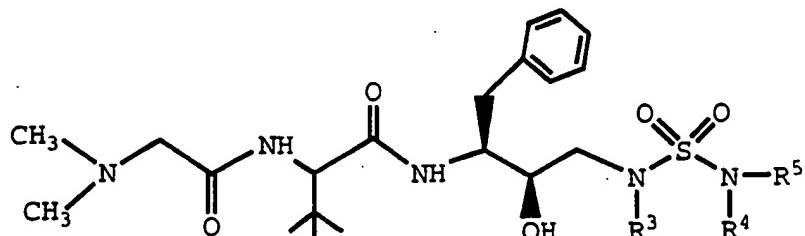
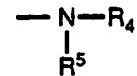
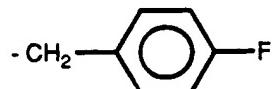
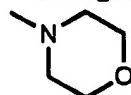
TABLE 16 R_3  $-\text{CH}_2\text{CH}(\text{CH}_3)_2$ $-\text{N}(\text{CH}_3)_2$ $-\text{CH}_2\text{CH}(\text{CH}_3)_2$ $-\text{N}(\text{CH}_2\text{CH}_3)_2$ $-\text{CH}_2\text{CH}(\text{CH}_3)_2$ $-\text{N}(\text{CH}(\text{CH}_3)_2)_2$ $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$ $-\text{N}(\text{CH}_3)_2$ $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$ $-\text{N}(\text{CH}_2\text{CH}_3)_2$ $-\text{CH}_2\text{CH}_2\text{CH}(\text{CH}_3)_2$  $-\text{N}(\text{CH}_3)_2$ $-\text{N}(\text{CH}_2\text{CH}_3)_2$

TABLE 16 (Cont'd.)

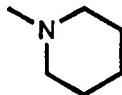
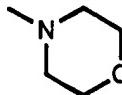
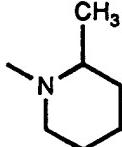
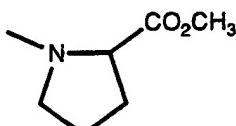
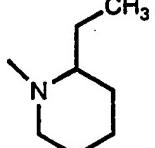
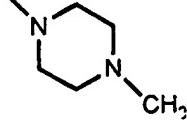
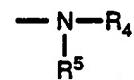
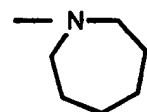
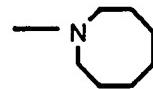
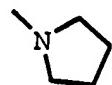
R_3	$\begin{array}{c} \text{---N---R}_4 \\ \\ \text{R}^5 \end{array}$
$-\text{CH}_2-\text{C}_6\text{H}_4-\text{F}$	
$-\text{CH}_2-\text{C}_6\text{H}_4-\text{F}$	
$-\text{CH}_2-\text{C}_6\text{H}_4-\text{F}$	$N(\text{CH}_3)(t\text{-Bu})$
$-\text{CH}_2-\text{C}_6\text{H}_4-\text{F}$	
$-\text{CH}_2-\text{C}_6\text{H}_4-\text{F}$	
$-\text{CH}_2-\text{C}_6\text{H}_4-\text{F}$	
$-\text{CH}_2-\text{C}_6\text{H}_4-\text{F}$	

TABLE 16 (Cont'd.)

 R_3  $-CH_2CH(CH_3)_2$  $-CH_2CH(CH_3)_2$  $-CH_2CH(CH_3)_2$ 

Example 22

The compounds of the present invention are effective HIV protease inhibitors. Utilizing an enzyme assay as described below, the compounds set forth in the examples herein disclosed inhibited the HIV enzyme. The preferred compounds of the present invention and their calculated IC₅₀ (inhibiting concentration 50%, i.e., the concentration at which the inhibitor compound reduces enzyme activity by 50%) values are shown in Table 17. The enzyme method is described below. The substrate is 2-Ile-Nle-Phe(p-NO₂)-Gln-ArgNH₂. The positive control is MVT-101 (Miller, M. et al, *Science*, 246, 1149 (1989)). The assay conditions are as follows:

15

Assay buffer: 20 mM sodium phosphate, pH 6.4
20% glycerol
1 mM EDTA
1 mM DTT
20 0.1% CHAPS

The above described substrate is dissolved in DMSO, then diluted 10 fold in assay buffer. Final substrate concentration in the assay is 80 μM.

25

HIV protease is diluted in the assay buffer to a final enzyme concentration of 12.3 nanomolar, based on a molecular weight of 10,780.

30

The final concentration of DMSO is 14% and the final concentration of glycerol is 18%. The test compound is dissolved in DMSO and diluted in DMSO to 10x the test concentration; 10μl of the enzyme preparation is added, the materials mixed and then the mixture is 35 incubated at ambient temperature for 15 minutes. The enzyme reaction is initiated by the addition of 40μl of

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substrate. The increase in fluorescence is monitored at 4 time points (0, 8, 16 and 24 minutes) at ambient temperature. Each assay is carried out in duplicate wells.

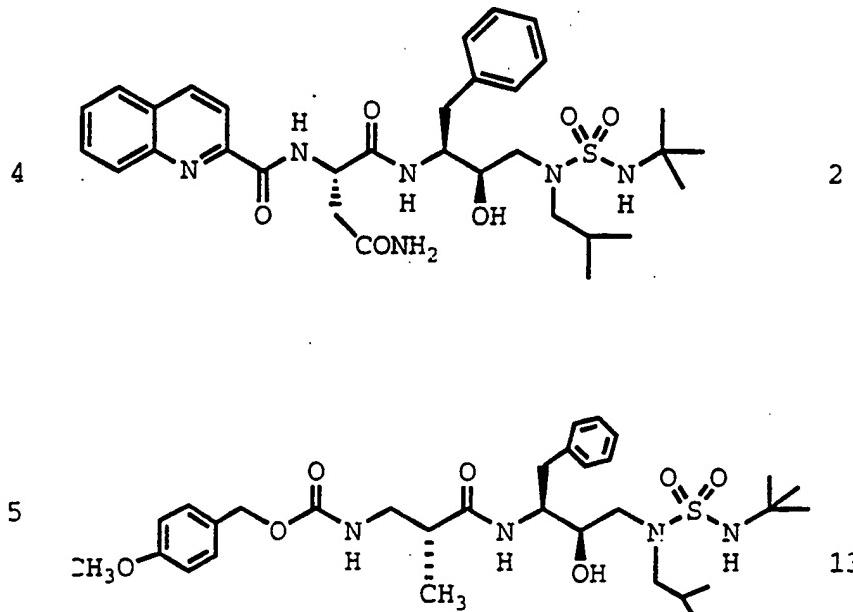
5

The preceding examples can be repeated with similar success by substituting the generically or specifically described reactants and/or operating conditions of this invention for those used in the 10 preceding examples.

TABLE 17

15 Entry	Compound	IC ₅₀ (nanomolar)
1		40
2		5
3		3

115



5

Example 23

The effectiveness of the compounds listed in
10 Table 17 were determined in the above-described enzyme
assay and in a CEM cell assay.

The HIV inhibition assay method of acutely
infected cells is an automated tetrazolium based
15 colorimetric assay essentially that reported by Pauwles
et al, *J. Virol. Methods*, 20, 309-321 (1988). Assays
were performed in 96-well tissue culture plates. CEM
cells, a CD4⁺ cell line, were grown in RPMI-1640 medium
(Gibco) supplemented with a 10% fetal calf serum and were
20 then treated with polybrene (2 μ g/ml). An 80 μ l volume of
medium containing 1 x 10⁴ cells was dispensed into each
well of the tissue culture plate. To each well was added
a 100 μ l volume of test compound dissolved in tissue
culture medium (or medium without test compound as a
25 control) to achieve the desired final concentration and

the cells were incubated at 37°C for 1 hour. A frozen culture of HIV-1 was diluted in culture medium to a concentration of 5×10^4 TCID₅₀ per ml (TCID₅₀ = the dose of virus that infects 50% of cells in tissue culture), 5 and a 20µL volume of the virus sample (containing 1000 TCID₅₀ of virus) was added to wells containing test compound and to wells containing only medium (infected control cells). Several wells received culture medium without virus (uninfected control cells). Likewise, the 10 intrinsic toxicity of the test compound was determined by adding medium without virus to several wells containing test compound. In summary, the tissue culture plates contained the following experiments:

15

Virus	Cells		Drug	
	1.	2.	3.	4.
20	+	-	-	-
	+	+	-	-
	+	-	+	
	+	+	+	+

25 In experiments 2 and 4 the final concentrations of test compounds were 1, 10, 100 and 500 µg/ml. Either azidothymidine (AZT) or dideoxyinosine (ddI) was included as a positive drug control. Test compounds were dissolved in DMSO and diluted into tissue culture medium 30 so that the final DMSO concentration did not exceed 1.5% in any case. DMSO was added to all control wells at an appropriate concentration.

Following the addition of virus, cells were 35 incubated at 37°C in a humidified, 5% CO₂ atmosphere for 7 days. Test compounds could be added on days 0, 2 and 5 if desired. On day 7, post-infection, the cells in each well were resuspended and a 100µl sample of each cell

suspension was removed for assay. A 20 μ L volume of a 5 mg/ml solution of 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) was added to each 100 μ L cell suspension, and the cells were incubated for 4 hours 5 at 27°C in a 5% CO₂ environment. During this incubation, MTT is metabolically reduced by living cells resulting in the production in the cell of a colored formazan product. To each sample was added 100 μ l of 10% sodium dodecylsulfate in 0.01 N HCl to lyse the cells, and 10 samples were incubated overnight. The absorbance at 590 nm was determined for each sample using a Molecular Devices microplate reader. Absorbance values for each set of wells is compared to assess viral control infection, uninfected control cell response as well as 15 test compound by cytotoxicity and antiviral efficacy.

The biological data shown in Tables 18 and 19 were obtained from the compounds shown in Tables 1C and 3B, respectively.

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TABLE 18

	<u>Entry Table 1C</u>	<u>IC₅₀ or % Inhibition</u>	<u>EC₅₀</u>	<u>TD₅₀</u>
	A	29% @ 0.1 uM		
5	B	55% @ 10.0 uM		
10	C	59% @ 1.0 uM		
	D	29% @ 0.1 uM		
15	E	70 nM	880 nM	7.5 uM
	F	22% @ 0.1 uM		
20	G	66 nM		
	H	48% @ 10.0 uM		
	I	1.7 uM		
25	J	2.69 uM		
	K	60% @ 1.0 uM		
30	L	38% @ 10.0 uM		

TABLE 19

	<u>Entry Table 3B</u>	<u>IC₅₀ (nM)</u>	<u>EC₅₀ (nM)</u>	<u>TD₅₀ (μM)</u>
	A	20		
40	B	27		
	C	42	350	>100
45	D	4.4	27	289
	E	4.0	13	8.3
	F	6.6	17	77

TABLE 20

Entry	Compound	IC ₅₀ (nm)	EC ₅₀ (nm)	TD ₅₀ (nm)
5				
1		40	167	56,000
2		5	23	65,000
3		3	42	28,000
4		2	<15	39,000

10

The compounds of the present invention are effective antiviral compounds and, in particular, are effective retroviral inhibitors as shown above. Thus, the subject compounds are effective HIV protease inhibitors.

- It is contemplated that the subject compounds will also inhibit other retroviruses such as other lentiviruses in particular other strains of HIV, e.g. HIV-2, human T-cell leukemia virus, respiratory syncitial virus, simian immunodeficiency virus, feline leukemia virus, feline immuno-deficiency virus, hepadnavirus, cytomegalovirus and picornavirus. Thus, the subject compounds are effective in the treatment and/or prophylaxis of retroviral infections.
- 10 Compounds of the present invention can possess one or more asymmetric carbon atoms and are thus capable of existing in the form of optical isomers as well as in the form of racemic or nonracemic mixtures thereof. The optical isomers can be obtained by resolution of the
- 15 racemic mixtures according to conventional processes, for example by formation of diastereoisomeric salts by treatment with an optically active acid or base. Examples of appropriate acids are tartaric, diacetyl tartaric, dibenzoyl tartaric, ditoluoyl tartaric and camphorsulfonic
- 20 acid and then separation of the mixture of diastereoisomers by crystallization followed by liberation of the optically active bases from these salts. A different process for separation of optical isomers involves the use of a chiral chromatography column optimally chosen to maximize the
- 25 separation of the enantiomers. Still another available method involves synthesis of covalent diastereoisomeric molecules by reacting compounds of Formula I with an optically pure acid in an activated form or an optically pure isocyanate. The synthesized diastereoisomers can be
- 30 separated by conventional means such as chromatography, distillation, crystallization or sublimation, and then hydrolyzed to deliver the enantiomerically pure compound. The optically active compounds of Formula I can likewise be obtained by utilizing optically active starting materials.
- 35 These isomers may be in the form of a free acid, a free base, an ester or a salt.

The compounds of the present invention can be used in the form of salts derived from inorganic or organic acids. These salts include but are not limited to the following: acetate, adipate, alginate, citrate, aspartate, benzoate, benzenesulfonate, bisulfate, butyrate, camphorate, camphorsulfonate, digluconate, cyclopentanepropionate, dodecylsulfate, ethanesulfonate, glucoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, fumarate, hydrochloride, hydrobromide, hydroiodide, 2-hydroxy-ethanesulfonate, lactate, maleate, methanesulfonate, nicotinate, 2-naphthalenesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, propionate, succinate, tartrate, thiocyanate, tosylate, mesylate and undecanoate. Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides, and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

25

Examples of acids which may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals, such as sodium, potassium, calcium or magnesium or with organic bases.

35

Total daily dose administered to a host in single or divided doses may be in amounts, for example, from 0.001

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to 50 mg/kg body weight daily and more usually 0.01 to 1 mg. Dosage unit compositions may contain such amounts of submultiples thereof to make up the daily dose.

5 The amount of active ingredient that may be combined with the carrier materials to produce a single dosage form will vary depending upon the host treated and the particular mode of administration.

10 The dosage regimen for treating a disease condition with the compounds and/or compositions of this invention is selected in accordance with a variety of factors, including the type, age, weight, sex, diet and medical condition of the patient, the severity of the
15 disease, the route of administration, pharmacological considerations such as the activity, efficacy, pharmacokinetic and toxicology profiles of the particular compound employed, whether a drug delivery system is utilized and whether the compound is administered as part
20 of a drug combination. Thus, the dosage regimen actually employed may vary widely and therefore may deviate from the preferred dosage regimen set forth above.

25 The compounds of the present invention may be administered orally, parenterally, by inhalation spray, rectally, or topically in dosage unit formulations containing conventional nontoxic pharmaceutically acceptable carriers, adjuvants, and vehicles as desired. Topical administration may also involve the use of
30 transdermal administration such as transdermal patches or iontophoresis devices. The term parenteral as used herein includes subcutaneous injections, intravenous, intramuscular, intrasternal injection, or infusion techniques.

- injectable aqueous or oleaginous suspensions may be formulated according to the known art using suitable dispersing or wetting agents and suspending agents. The sterile injectable preparation may also be a sterile
- 5 injectable solution or suspension in a nontoxic parenterally acceptable diluent or solvent, for example, as a solution in 1,3-butanediol. Among the acceptable vehicles and solvents that may be employed are water, Ringer's solution, and isotonic sodium chloride solution.
- 10 In addition, sterile, fixed oils are conventionally employed as a solvent or suspending medium. For this purpose any bland fixed oil may be employed including synthetic mono- or diglycerides. In addition, fatty acids such as oleic acid find use in the preparation of
- 15 injectables.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable nonirritating excipient such as cocoa butter and

20 polyethylene glycols which are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

Solid dosage forms for oral administration may

25 include capsules, tablets, pills, powders, and granules. In such solid dosage forms, the active compound may be admixed with at least one inert diluent such as sucrose lactose or starch. Such dosage forms may also comprise, as in normal practice, additional substances other than inert

30 diluents, e.g., lubricating agents such as magnesium stearate. In the case of capsules, tablets, and pills, the dosage forms may also comprise buffering agents. Tablets and pills can additionally be prepared with enteric coatings.

include pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art, such as water. Such compositions may also comprise adjuvants, such as wetting agents, 5 emulsifying and suspending agents, and sweetening, flavoring, and perfuming agents.

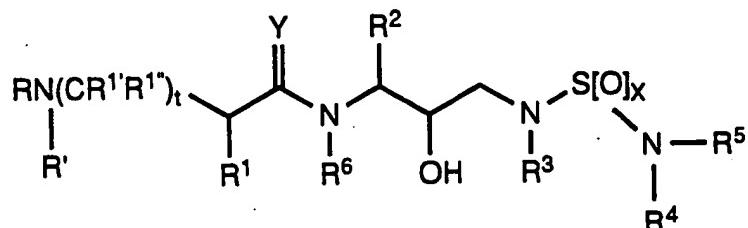
While the compounds of the invention can be administered as the sole active pharmaceutical agent, they 10 can also be used in combination with one or more immunomodulators, antiviral agents or other antiinfective agents. For example, the compounds of the invention can be administered in combination with AZT, DDI, DDC or with glucosidase inhibitors, such as N-butyl-1-deoxynojirimycin 15 or prodrugs thereof, for the prophylaxis and/or treatment of AIDS. When administered as a combination, the therapeutic agents can be formulated as separate compositions which are given at the same time or different times, or the therapeutic agents can be given as a single 20 composition.

The foregoing is merely illustrative of the invention and is not intended to limit the invention to the disclosed compounds. Variations and changes which are 25 obvious to one skilled in the art are intended to be within the scope and nature of the invention which are defined in the appended claims.

From the foregoing description, one skilled in 30 the art can easily ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions.

WHAT IS CLAIMED IS:

1. A compound represented by the formula:



5

or a pharmaceutically acceptable salt, prodrug or ester thereof wherein:

- 10 R represents hydrogen, alkyl, alkenyl, alkynyl, cycloalkyl, aryl, aralkyl, alkoxycarbonyl, aryloxalkyl, heteroaryloxalkyl, aralkoxycarbonyl, alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, arakanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxalkanoyl, heterocyclcarbonyl, heterocycloxycarbonyl, heterocyclalkanoyl, heterocyclalkoxycarbonyl, heteroaralkanoyl, heteroaralkoxycarbonyl, heteroaryloxy-carbonyl, heteroaroyl, alkoxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, heterocycloalkyl radicals, or wherein said aminocarbonyl and aminoalkanoyl radicals are disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;
- 20
- 25
- 30 R' represents hydrogen and radicals as defined for R³ or R"SO₂- wherein R" represents radicals as defined for R³;

or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

- 5 R¹ represents hydrogen, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃, -CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid side chains selected from asparagine, S-methyl cysteine
10 and methionine and the sulfoxide (SO) and sulfone (SO₂) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, allo-threonine, serine, O-alkyl serine, aspartic acid,
15 beta-cyano alanine and valine side chains;

- R^{1'} and R^{1''} independently represent hydrogen and radicals as defined for R¹, or one of R^{1'} and R^{1''}, together with R¹ and the carbon atoms to which R¹, R^{1'} and R^{1''} are attached, represent a cycloalkyl radical;

- R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, -NO₂, -C≡N, CF₃, -OR⁹, -SR⁹, wherein R⁹ represents hydrogen and alkyl radicals;

- R³ represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said

substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone or sulfoxide derivatives
5 thereof;

R⁴ and R⁵ independently represent hydrogen and radicals as defined by R³ or together with a nitrogen atom to which they are bonded form a heterocycloalkyl or a
10 heteroaryl radical;

R⁶ represents hydrogen and alkyl radicals;

x represents 1 or 2;

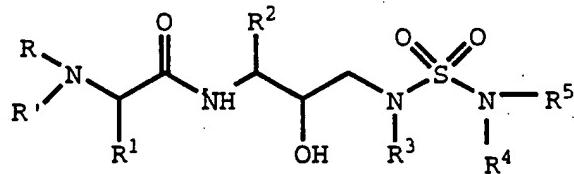
15

t represents either 0, 1 or 2; and

Y represents O, S and NR¹⁵ wherein R¹⁵ represents hydrogen and radicals as defined for R³.

20

2. Compound represented by the formula:



25 wherein:

R represents hydrogen, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, alkoxyalkyl, hydroxyalkyl, alkoxycarbonyl, aralkoxycarbonyl,
30 alkylcarbonyl, cycloalkylcarbonyl, cycloalkylalkoxycarbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxcarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclcarbonyl, heterocyclloxycarbonyl, heterocyclalkanoyl.

heterocyclalkoxycarbonyl, heteroaralkancyl,
heteroaralkoxycarbonyl, heteroaryloxycarbonyl,
heteroaroyl, aminocarbonyl, aminoalkanoyl, and mono- and
disubstituted aminocarbonyl and mono- and disubstituted
5 aminoalkanoyl radicals wherein the substituents are
selected from alkyl, aryl, aralkyl, cycloalkyl,
cycloalkylalkyl, heteroaryl, heteroaralkyl,
heterocycloalkyl, heterocycloalkyalkyl radicals, or where
said aminoalkanoyl radical is disubstituted, said
10 substituents along with the nitrogen atom to which they
are attached form a heterocycloalkyl or heteroaryl
radical;

R' represents hydrogen and radicals as defined for R³ or
15 R and R' together with the nitrogen to which they are
attached represent heterocycloalkyl and heteroaryl
radical;

R¹ represents hydrogen, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃,
20 -CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃),
-C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl,
alkenyl, alkynyl and cycloalkyl radicals, and amino acid
side chains selected from asparagine, S-methyl cysteine
and methionine and the sulfoxide (SO) and sulfone (SO₂)
25 derivatives thereof, isoleucine, allo-isoleucine,
alanine, leucine, tert-leucine, phenylalanine, ornithine,
histidine, norleucine, glutamine, threonine, glycine,
allo-threonine, serine, O-methyl serine, aspartic acid,
beta-cyanoalanine and valine side chains;

30 R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl
and aralkyl radicals, which radicals are optionally
substituted with a group selected from alkyl and halogen
radicals, -NO₂, -C≡N, CF₃, -OR⁹, -SR⁹, wherein R⁹
35 represents hydrogen and alkyl radicals;

- R³ represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone or sulfoxide derivatives thereof;
- 15 R⁴ and R⁵ independently represent hydrogen and radicals as defined by R³, or together with the nitrogen atom to which they are bonded represent heterocycloalkyl and heteroaryl radicals.
- 20 3. Compound of Claim 2 wherein R represents aralkoxycarbonyl and heteroaroyl radicals.
- 25 4. Compound of Claim 2 wherein R represents carbobenzoxy, 2-benzofurancarbonyl and 2-quinolinylcarbonyl radicals.
- 30 5. Compound of Claim 2 where R represents acetyl, N,N-dimethylaminoacetyl, N-methylaminoacetyl or N-benzyl-N-methylaminoacetyl.
- 35 6. Compound of Claim 2 wherein R¹ represents alkyl, alkynyl and alkenyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, threonine, allo-threonine, isoleucine, S-methyl

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cysteine and the sulfone and sulfoxide derivatives thereof, alanine, and allo-isoleucine.

7. Compound of Claim 2 wherein R¹ represents
5 methyl, propargyl, t-butyl, isopropyl and sec-butyl radicals, and amino acid side chains selected from the group consisting of asparagine, valine, S-methyl cysteine, allo-iso-leucine, iso-leucine, threonine, serine, aspartic acid, beta-cyano alanine, and allo-
10 threonine side chains.

8. Compound of Claim 2 wherein R² represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals
15 and radicals represented by the formula -OR⁹ and -SR⁹ wherein R⁹ represents hydrogen and alkyl radicals.

9. Compound of Claim 2 wherein R² represents alkyl, cycloalkylalkyl and aralkyl radicals.
20

10. Compound of Claim 2 wherein R² represents CH₃SCH₂CH₂-, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals.

25 11. Compound of Claim 2 wherein R³ independently represents alkyl, haloalkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals.

30 12. Compound of Claim 2 wherein R³ represents alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals.
35

13. Compound of Claim 2 wherein R³ and R⁴ independently represent alkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.

5 14. Compound of Claim 2 wherein R³ represents isobutyl, n-propyl, isopropyl, n-butyl, isoamyl, cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl radicals.

10 15. Compound of Claim 2 wherein R³ is an isobutyl, n-butyl or isoamyl radical and R⁴ is a tertiary-butyl radical.

15 16. Compound of Claim 2 wherein R³ is an isobutyl, n-butyl or isoamyl radical and R⁴ is a phenyl radical.

20 17. Compound of Claim 2 wherein R⁴ and R⁵ independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.

25 18. Compound of Claim 2 wherein R⁴ and R⁵ independently represent hydrogen, alkyl and aryl radicals.

30 19. Compound of Claim 2 wherein R⁴ and R⁵ independently represent hydrogen, methyl, ethyl, isopropyl, n-butyl, t-butyl, 1,1-dimethylpropyl, cyclohexyl and phenyl radicals.

35 20. Compound of Claim 2 wherein R⁴ and R⁵ together with the nitrogen atom to which they are bonded form a heterocyloalkyl or heteroaryl radical.

21. Compound of Claim 2 wherein R⁴ and R⁵ together with the nitrogen atom to which they are bonded form a heterocycloalkyl or heteroaryl radical having from 4 to 8 ring members.

5

22. Compound of Claim 2 wherein R⁴ and R⁵ together with the nitrogen atom to which they are bonded form a pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl radical.

10

23. A pharmaceutical composition comprising a compound of Claim 1 and a pharmaceutically acceptable carrier.

15

24. A pharmaceutical composition comprising a compound of Claim 2 and a pharmaceutically acceptable carrier.

20

25. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 23.

25

26. Method of Claim 25 wherein the retroviral protease is HIV protease.

30

27. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 23.

35

28. Method of Claim 27 wherein the retroviral infection is an HIV infection.

29. Method for treating AIDS comprising administering an effective amount of a composition of
Claim 23.

30. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 24.

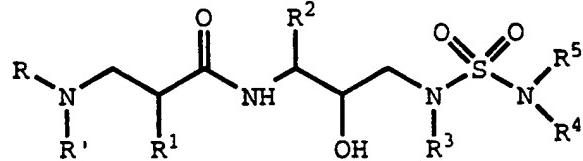
5 31. Method of Claim 30 wherein the retroviral protease is HIV protease.

10 32. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 24.

33. Method of Claim 30 wherein the retroviral infection is an HIV infection.

15 34. Method for treating AIDS comprising administering an effective amount of a composition of Claim 24.

20 35. Compound represented by the formula:



wherein:

25 R represents hydrogen, alkoxy carbonyl, aralkoxy carbonyl, alkyl carbonyl, cycloalkyl carbonyl, cycloalkylalkoxy carbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclic carbonyl, heterocyclicloxy carbonyl, heterocycliclalkanoyl, heterocyclicloxy carbonyl, heterocycliclalkanoyl, heteroaralkoxy carbonyl, heteroaralkanoyl, heteroaralkoxy carbonyl, heteroaryloxy carbonyl, heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl, aryloxyalkyl, heteroaryloxyalkyl, alkoxyalkyl, hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and

disubstituted aminocarbonyl and mono- and disubstituted aminoalkanoyl radicals wherein the substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl,

- 5 heterocycloalkyl, heterocycloalkyalkyl radicals, or where said aminoalkanoyl radical is disubstituted, said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

10

R' represents hydrogen and radicals as defined for R³ or R and R' together with the nitrogen to which they are attached represent heterocycloalkyl and heteroaryl radical;

15

R¹ represents hydrogen, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃, -CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃),

-C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl, alkenyl, alkynyl and cycloalkyl radicals, and amino acid

- 20 side chains selected from asparagine, S-methyl cysteine and methionine and the sulfoxide (SO) and sulfone (SO₂) derivatives thereof, isoleucine, allo-isoleucine, alanine, leucine, tert-leucine, phenylalanine, ornithine, histidine, norleucine, glutamine, threonine, glycine, 25 allo-threonine, serine, aspartic acid, beta-cyanoalanine and valine side chains;

R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally

- 30 substituted with a group selected from alkyl and halogen radicals, -NO₂, -C≡N, CF₃, -OR⁹, -SR⁹, wherein R⁹ represents hydrogen and alkyl radicals;

R³ represents alkyl, haloalkyl, alkenyl, alkynyl,

- 35 hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl,

aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl,
5 heterocycloalkyl, and heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl
10 radicals and the sulfone or sulfoxide derivatives thereof;

R⁴ and R⁵ independently represent hydrogen and radicals as defined by R³, or together with the nitrogen atom to
15 which they are bonded represent heterocycloalkyl and heteroaryl radicals.

36. Compound of Claim 35 wherein R¹ represents hydrogen, alkyl, alkenyl and alkynyl radicals.

20

37. Compound of Claim 35 wherein R¹ represents methyl, ethyl, isopropyl, propargyl and t-butyl radicals.

38. Compound of Claim 35 wherein R' is
25 hydrogen and R is NH₂C^O or CH₃NH—C^O—.

39. Compound of Claim 35 wherein R' is hydrogen and R represents acetyl, phenoxyacetyl, 2-naphthoxy-carbonyl, benzyloxycarbonyl,
30 p-methoxybenzyloxycarbonyl.

40. Compound of Claim 35 wherein R and R' are independently selected from methyl and phenethyl radicals.

41. Compound of Claim 35 wherein R² represents alkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with halogen radicals and radicals represented by the formula -OR⁹ and -SR⁹ 5 wherein R⁹ represents hydrogen and alkyl radicals.

42. Compound of Claim 35 wherein R² represents alkyl, cycloalkylalkyl and aralkyl radicals.

10 43. Compound of Claim 35 wherein R² represents CH₃SCH₂CH₂-, iso-butyl, n-butyl, benzyl, 4-fluorobenzyl, 2-naphthylmethyl and cyclohexylmethyl radicals.

15 44. Compound of Claim 35 wherein R² represents benzyl, 4-fluorobenzyl, and 2-naphthylmethyl radicals.

20 45. Compound of Claim 35 wherein R³ independently represents alkyl, haloalkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl and heteroaralkyl radicals.

25 46. Compound of Claim 35 wherein R³ represents alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl radicals.

30 47. Compound of Claim 35 wherein R³ and R⁴ independently represent alkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.

35 48. Compound of Claim 35 wherein R³ represents isobutyl, n-propyl, isopropyl, n-butyl, isoamyl, cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl radicals.

49. Compound of Claim 35 wherein R³ is an isobutyl, n-butyl or t-butyl radical and R⁴ is a t-butyl radical.

5 50. Compound of Claim 35 wherein R³ is an isobutyl, n-butyl or isoamyl radical and R⁴ is a phenyl radical.

10 51. Compound of Claim 35 wherein R⁴ and R⁵ independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.

15 52. Compound of Claim 35 wherein R⁴ and R⁵ independently represent hydrogen, alkyl and aryl radicals.

20 53. Compound of Claim 35 wherein R⁴ and R⁵ independently represent hydrogen, methyl, ethyl, isopropyl, n-butyl, cyclohexyl, t-butyl, 1,1-dimethylpropyl and phenyl radicals.

25 54. Compound of Claim 35 wherein R⁴ and R⁵ together with the nitrogen atom to which they are bonded form a heterocyloalkyl or heteroaryl radical.

30 55. Compound of Claim 35 wherein R⁴ and R⁵ together with the nitrogen atom to which they are bonded form a heterocycloalkyl or heteroaryl radical having from 4 to 8 ring members.

35 56. Compound of Claim 35 wherein R⁴ and R⁵ together with the nitrogen atom to which they are bonded form a pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl radical.

57. A pharmaceutical composition comprising a compound of Claim 35 and a pharmaceutically acceptable carrier.

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58. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 57.

10

59. Method of Claim 58 wherein the retroviral protease is HIV protease.

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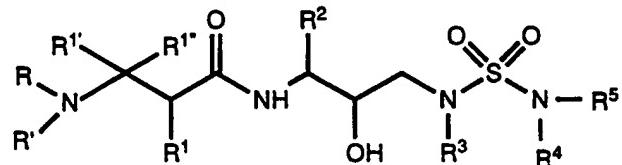
60. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 57.

61. Method of Claim 60 wherein the retroviral infection is an HIV infection.

20

62. Method for treating AIDS comprising administering an effective amount of a composition of Claim 57.

25



wherein:

30 R represents hydrogen, alkoxy carbonyl, aralkoxy carbonyl, alkyl carbonyl, cycloalkyl carbonyl, cycloalkylalkoxy carbonyl, cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl, aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl, heterocyclic carbonyl, heterocyclic alkyl, heterocyclic alkoxy carbonyl, heterocyclic alkanyl,

- heterocyclalkoxycarbonyl, heteroaralkanoyl,
heteroaralkoxycarbonyl, heteroaryloxy-carbonyl,
heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl, aralkyl,
aryloxyalkyl, heteroaryloxyalkyl, alkoxyalkyl,
- 5 hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and
disubstituted aminocarbonyl and mono- and disubstituted
aminoalkanoyl radicals wherein the substituents are
selected from alkyl, aryl, aralkyl, cycloalkyl,
cycloalkylalkyl, heteroaryl, heteroaralkyl,
- 10 heterocycloalkyl, heterocycloalkyalkyl radicals, or where
said aminoalkanoyl radical is disubstituted, said
substituents along with the nitrogen atom to which they
are attached form a heterocycloalkyl or heteroaryl
radical;
- 15 R' represents hydrogen and radicals as defined for R³ or
R and R' together with the nitrogen to which they are
attached represent heterocycloalkyl and heteroaryl
radical;
- 20 R¹ represents hydrogen, -CH₂SO₂NH₂, -CH₂CO₂CH₃, -CO₂CH₃,
-CONH₂, -CH₂C(O)NHCH₃, -C(CH₃)₂(SH), -C(CH₃)₂(SCH₃),
-C(CH₃)₂(S[O]CH₃), -C(CH₃)₂(S[O]₂CH₃), alkyl, haloalkyl,
alkenyl, alkynyl and cycloalkyl radicals, and amino acid
25 side chains selected from asparagine, S-methyl cysteine
and methionine and the sulfoxide (SO) and sulfone (SO₂)
derivatives thereof, isoleucine, allo-isoleucine,
alanine, leucine, tert-leucine, phenylalanine, ornithine,
histidine, norleucine, glutamine, threonine, glycine,
30 allo-threonine, serine, aspartic acid, beta-cyano alanine
and valine side chains;
- R^{1'} and R^{1''} independently represent hydrogen and radicals
as defined for R¹, or one of R^{1'} and R^{1''}, together with
35 R¹ and the carbon atoms to which R¹, R^{1'} and R^{1''} are
attached, represent a cycloalkyl radical;

140

R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radials, -NO₂, -C≡N, CF₃, -OR⁹, -SR⁹, wherein R⁹

5 represents hydrogen and alkyl radicals;

R³ represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, heterocycloalkylalkyl,

10 aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said

substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or

15 in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone or sulfoxide derivatives

20 thereof;

R⁴ and R⁵ independently represent hydrogen and radicals as defined by R³, or together with the nitrogen atom to which they are bonded represent heterocycloalkyl and

25 heteroaryl radicals.

64. Compound of Claim 63 wherein R' represents hydrogen and R represents aralkoxycarbonyl and heteroaroyl radicals.

30

65. Compound of Claim 63 wherein R' is hydrogen and R represents carbobenzoxy, 2-benzofurancarbonyl, and 2-quinolinylcarbonyl radicals.

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66. Compound of Claim 63 wherein R' is hydrogen and R is 2-quinolinylcarbonyl.

67. Compound of Claim 63 wherein R¹, R^{1'} and R^{1''} independently represent hydrogen and alkyl radicals having from 1 to about 4 carbon atoms, alkenyl, alkynyl, 5 aralkyl radicals and radicals selected from -CH₂SO₂NH₂, -CO₂CH₃, -CONHCH₃, -CON(CH₃)₂, -CH₂C(O)NHCH₃, -CH₂C(O)N(CH₃)₂, -CONH₂, -C(CH₃)₂(SCH₃), -C(CH₃)₂(S[O]CH₃) and -C(CH₃)₂(S[O]CH₃).
- 10 68. Compound of Claim 63 wherein R¹, R^{1'} and R^{1''} independently represent hydrogen, methyl, ethyl, benzyl, phenylpropyl, propargyl, hydroxyl and radicals selected from -C(O)OCH₃, -C(O)NH₂, -C(O)OH.
- 15 69. Compound of Claim 63 wherein R¹ and R^{1'} are both hydrogen and R^{1''} is C(O)NH₂.
70. Compound of Claim 63 wherein R represents aralkoxycarbonyl and heteroaroyl radicals.
- 20 71. Compound of Claim 63 wherein R¹ and R^{1'} are both hydrogen and R^{1''} is methyl.
72. Compound of Claim 63 wherein R^{1'} is 25 hydrogen and R¹ and R^{1''} together with the carbon atoms to which they are attached form a three to six-membered cycloalkyl radical.
- 30 73. Compound of Claim 63 wherein R is carbobenzoxy, 2-quinolinylcarbonyl and 2-benzofuran carbonyl radicals.
74. Compound of Claim 63 wherein R¹ and R^{1'} are both hydrogen and R^{1''} is propargyl.
- 35 75. Compound of Claim 63 wherein R² represents alkyl, cycloalkylalkyl and aralkyl radicals, which

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radicals are optionally substituted with halogen radicals and radicals represented by the formula -CR⁹ and -SR⁹ wherein R⁹ represents hydrogen and alkyl radicals.

5 76. Compound of Claim 63 wherein R² represents alkyl, cycloalkylalkyl and aralkyl radicals.

77. Compound of Claim 63 wherein R² represents aralkyl radicals.

10

78. Compound of Claim 63 wherein R³ independently represents alkyl, haloalkyl, alkenyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heterocycloalkylalkyl, aryl, aralkyl 15 and heteroaralkyl radicals.

79. Compound of Claim 63 wherein R³ represents alkyl, cycloalkyl, cycloalkylalkyl, aralkyl, heteroaralkyl, heterocycloalkyl, heterocycloalkylalkyl 20 radicals.

80. Compound of Claim 63 wherein R³ and R⁴ independently represent alkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.

25

81. Compound of Claim 63 wherein R³ represents isobutyl, n-propyl, isopropyl, n-butyl, isoamyl, cyclohexyl, cyclohexylmethyl, benzyl and pyridylmethyl radicals.

30

82. Compound of Claim 63 wherein R³ is an isobutyl, n-butyl or isoamyl radical and R⁴ is a tert-butyl radical.

83. Compound of Claim 63 wherein R³ is an isobutyl, n-butyl or isoamyl radical and R⁴ is a phenyl radical.

5 84. Compound of Claim 63 wherein R⁴ and R⁵ independently represent hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, aryl, heteroaryl, aralkyl, heteroaralkyl, heterocycloalkyl and heterocycloalkylalkyl radicals.

10

85. Compound of Claim 63 wherein R⁴ and R⁵ independently represent hydrogen, alkyl and aryl radicals.

15

86. Compound of Claim 63 wherein R⁴ and R⁵ independently represent hydrogen, methyl, ethyl, isopropyl, n-butyl, t-butyl, cyclohexyl, 1,1-dimethylpropyl and phenyl radicals.

20

87. Compound of Claim 63 wherein R⁴ and R⁵ together with the nitrogen atom to which they are bonded form a heterocyloalkyl or heteroaryl radical.

25

88. Compound of Claim 63 wherein R⁴ and R⁵ together with the nitrogen atom to which they are bonded form a heterocycloalkyl or heteroaryl radical having from 4 to 8 ring members.

30

89. Compound of Claim 63 wherein R⁴ and R⁵ together with the nitrogen atom to which they are bonded form a pyrrolidinyl, piperidinyl, morpholinyl or piperazinyl radical.

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90. A pharmaceutical composition comprising a compound of Claim 63 and a pharmaceutically acceptable carrier.

91. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 89.

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92. Method of Claim 90 wherein the retroviral protease is HIV protease.

10 93. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 89.

94. Method of Claim 92 wherein the retroviral infection is an HIV infection.

15

95. Method for treating AIDS comprising administering an effective amount of a composition of Claim 89.

20

96. A compound of Claim 1 which is:

N-[3-[(butylamino)sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-(dimethylamino)-1-oxoethyl)amino]dimethylbutanamide;

25

N-[3-[(methylamino)sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-(dimethylamino)-1-oxoethyl)amino]dimethylbutaneamide;

30

N1-[2R-hydroxy-3-[(4-methyl-1-piperazinyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide;

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N1-[3-[(butylamino)sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide;

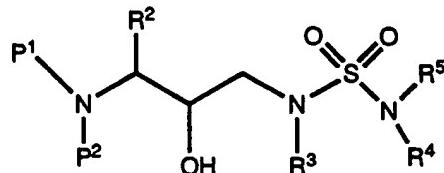
N1-[3-[(1,1-dimethylethyl)amino]sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide;

5 N'-[3-[(phenylamino)sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide; or

10 N'-[3-[(cyclohexylamino)sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl]-2S-[(2-quinolinylcarbonyl)amino]butanediamide.

97. A compound represented by the formula:

15



wherein:

P¹ and P² independently represent hydrogen,
20 alkoxy carbonyl, aralkoxy carbonyl, alkyl carbonyl,
cycloalkyl carbonyl, cycloalkylalkoxy carbonyl,
cycloalkylalkanoyl, alkanoyl, aralkanoyl, aroyl,
aryloxycarbonyl, aryloxycarbonylalkyl, aryloxyalkanoyl,
heterocyclcarbonyl, heterocyclloxy carbonyl,
25 heterocyclalkanoyl, heterocyclalkoxy carbonyl,
heteroaralkanoyl, heteroaralkoxy carbonyl, heteroaryloxy carbonyl,
heteroaroyl, alkyl, alkenyl, cycloalkyl, aryl,
aralkyl, aryloxyalkyl, heteroaryloxyalkyl, alkoxyalkyl,
hydroxyalkyl, aminocarbonyl, aminoalkanoyl, and mono- and
30 disubstituted aminocarbonyl and mono- and disubstituted
aminoalkanoyl radicals wherein the substituents are
selected from alkyl, aryl, aralkyl, cycloalkyl,
cycloalkylalkyl, heteroaryl, heteroaralkyl,
heterocycloalkyl, heterocycloalkylalkyl radicals, or where

said aminoalkanoyl radical is disubstituted said substituents along with the nitrogen atom to which they are attached form a heterocycloalkyl or heteroaryl radical;

5

R² represents alkyl, aryl, cycloalkyl, cycloalkylalkyl and aralkyl radicals, which radicals are optionally substituted with a group selected from alkyl and halogen radicals, -NO₂, -C≡N, CF₃, -OR⁹, -SR⁹, wherein R⁹

10 represents hydrogen and alkyl radicals;

R³ represents hydrogen, alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, heterocycloalkyl, heteroaryl, 15 heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and 20 heterocycloalkylalkyl radicals, or in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical, and thioalkyl, alkylthioalkyl and arylthioalkyl radicals and the sulfone 25 or sulfoxide derivatives thereof;

R⁴ and R⁵ independently represent hydrogen and radicals as defined by R³ or together with a nitrogen atom to which they are bonded form a heterocycloalkyl or a 30 heteroaryl radical.

98. Compound of Claim 97 wherein R³ represents alkyl, haloalkyl, alkenyl, alkynyl, hydroxyalkyl, alkoxyalkyl, cycloalkyl, cycloalkylalkyl, 35 heterocycloalkyl, heteroaryl, heterocycloalkylalkyl, aryl, aralkyl, heteroaralkyl, aminoalkyl and mono- and

- disubstituted aminoalkyl radicals, wherein said substituents are selected from alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heteroaryl, heteroaralkyl, heterocycloalkyl, and heterocycloalkylalkyl radicals, or
- 5 in the case of a disubstituted aminoalkyl radical, said substituents along with the nitrogen atom to which they are attached, form a heterocycloalkyl or a heteroaryl radical; and
- 10 R⁴ and R⁵ independently represent hydrogen and radicals as defined by R³, or together with the nitrogen atom to which they are bonded represent heterocycloalkyl and heteroaryl radicals.
- 15 99. A pharmaceutical composition comprising a compound of Claim 97 and a pharmaceutically acceptable carrier.
- 20 100. Method of inhibiting a retroviral protease comprising administering a protease inhibiting amount of a composition of Claim 99.
- 25 101. Method of Claim 100 wherein the retroviral protease is HIV protease.
102. Method of treating a retroviral infection comprising administering an effective amount of a composition of Claim 99.
- 30 103. Method of Claim 101 wherein the retroviral infection is an HIV infection.
- 35 104. Method for treating AIDS comprising administering an effective amount of a composition of Claim 99.

105. A compound of Claim 97 which is:

- phenylmethyl[2R-hydroxy-3-[(dimethylamino)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl] carbamate;
- 5 phenylmethyl[2R-hydroxy-3-[(dimethylamino)sulfonyl](3-methylbutyl)amino]-1S-(phenylmethyl)propyl] carbamate;
- 10 phenylmethyl [3-[(butylamino)sulfonyl](2-methylpropyl)amino]-2R-hydroxy-1S-(phenylmethyl)propyl] carbamate;
- 15 phenylmethyl [2R-hydroxy-3-[(4-methyl-1-piperazinyl)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl] carbamate;
- 20 phenylmethyl [2R-hydroxy-3-[(1,1-dimethyl)amino)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl] carbamate;
- 25 phenylmethyl [2R-hydroxy-3-[(methylethyl)amino]-sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl] carbamate;
- 30 phenylmethyl [2R-hydroxy-3-[(phenylamino)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl] carbamate;
- 35 phenylmethyl [2R-hydroxy-3-[(cyclohexylamino)sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl] carbamate;
or
phenylmethyl [2R-hydroxy-3-[(1-pyrrolidinyl)amino]-sulfonyl](2-methylpropyl)amino]-1S-(phenylmethyl)propyl] carbamate.

A. CLASSIFICATION OF SUBJECT MATTER					
IPC 5	C07C307/06	C07D295/22	C07K5/06	C07D215/48	A61K31/18
	A61K31/495	A61K31/45	A61K31/40	A61K37/02	

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07C C07D C07K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	GB,A,2 200 115 (SANDOZ) 27 July 1988 cited in the application see page 1 - page 5; examples 22-24,28 ----	1-24
X	EP,A,0 364 804 (ABBOTT LABORATORIES) 25 April 1990 see page 111, line 45 - page 112, line 29 ----	97,98
X	EP,A,0 468 641 (SHIONOGI) 29 January 1992 see pages 40-41, preparations 64,65 ----	97,98
A	WO,A,92 08699 (MONSANTO) 29 May 1992 see page 3 - page 5 -----	1-105

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

* Special categories of cited documents :

- "A" document defining the general state of the art which is not considered to be of particular relevance
- "B" earlier document but published on or after the international filing date
- "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- "O" document referring to an oral disclosure, use, exhibition or other means
- "P" document published prior to the international filing date but later than the priority date claimed

- "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- "&" document member of the same patent family

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Date of the actual completion of the international search

Date of mailing of the international search report

17 January 1994

- 4. 02. 94

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

PCT/US 93/ 10552

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 25-34, 58-62, 91-95, 100-104 are directed to a method of treatment of the human or animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. Claims Nos.: because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- The additional search fees were accompanied by the applicant's protest.
 No protest accompanied the payment of additional search fees.

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
GB-A-2200115	27-07-88	AU-A-	1037588	01-09-88
		BE-A-	1002212	16-10-90
		CH-A-	676988	28-03-91
		DE-A-	3800591	04-08-88
		FR-A-	2609716	22-07-88
		JP-A-	1019053	23-01-89
		LU-A-	87110	23-08-88
		NL-A-	8800100	16-08-88
		SE-A-	8800169	22-07-88
EP-A-0364804	25-04-90	AU-B-	639212	22-07-93
		AU-A-	4416389	01-05-90
		EP-A-	0437508	24-07-91
		JP-T-	4505608	01-10-92
		WO-A-	9003971	19-04-90
		US-A-	5268374	07-12-93
EP-A-0468641	29-01-92	AU-B-	4489093	25-11-93
		AU-B-	643036	04-11-93
		AU-A-	7930491	02-01-92
		CA-A-	2045008	29-12-91
		JP-A-	5009162	19-01-93
		US-A-	5194608	16-03-93
		US-A-	5272268	21-12-93
		US-A-	5223615	29-06-93
WO-A-9208699	29-05-92	AU-A-	9053191	11-06-92
		AU-A-	9085191	11-06-92
		AU-A-	9092591	11-06-92
		AU-A-	9125191	11-06-92
		AU-A-	9133291	11-06-92
		CA-A-	2096407	20-05-92
		CA-A-	2096409	20-05-92
		CA-A-	2096525	20-05-92
		CA-A-	2096528	20-05-92
		EP-A-	0558603	08-09-93
		EP-A-	0554400	11-08-93
		EP-A-	0558630	08-09-93
		EP-A-	0558657	08-09-93
		EP-A-	0558673	08-09-93

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9208699		WO-A- 9208698	29-05-92
		WO-A- 9208700	29-05-92
		WO-A- 9208701	29-05-92
		WO-A- 9208688	29-05-92